



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61M 5/24, 5/19, 5/178		A1	(11) International Publication Number: WO 00/29049
			(43) International Publication Date: 25 May 2000 (25.05.00)
<p>(21) International Application Number: PCT/US99/26751</p> <p>(22) International Filing Date: 12 November 1999 (12.11.99)</p> <p>(30) Priority Data: 60/108,382 13 November 1998 (13.11.98) US 60/131,644 29 April 1999 (29.04.99) US</p> <p>(71) Applicant (for all designated States except US): ELAN PHARMA INTERNATIONAL LIMITED [IE/IE]; Lincoln House, Lincoln Place, Dublin 2 (IE).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): LAVI, Gilad [IL/IL]; Harav Bazov David 6, 58497 Holon (IL). YIGAL, Gil [IL/IL]; Shlom Zion 5/7, Gan-Yavne 60800 (IL). TSALS, Izrafil [US/US]; 17 Rose Way, Sudbury, MA 01776 (US). GROSS, Yossi [IL/IL]; Moshav Mazor 20502 (IL).</p> <p>(74) Agents: HOOVER, Thomas, O. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).</p>			<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. With amended claims.</p>
<p>(54) Title: DRUG DELIVERY SYSTEMS AND METHODS</p> <p>(57) Abstract</p> <p>The present invention relates to a drug delivery device for mixing and delivering a drug by injection. The device includes a housing having a first port or opening therein that receives a first container that contains a fluid or powdered drug, for example, a lyophilized drug. The housing can also include a second port or opening that receives a second container that contains a fluid to be mixed with the drug to form an injectable fluid. The device includes a manifold having a channel that fluidly connects the first and second containers. A penetrating membrane such as a needle is used to inject the drug into a patient which is in fluid communication with the first container. The needle is movable from a storage position in the housing to an injection position extending through the housing.</p>			

DRUG DELIVERY SYSTEMS AND METHODS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/108,382 filed November 13, 1998 and U.S. Provisional Application No. 5 60/131,644 filed April 29, 1999, the entire teachings of both of these applications being incorporated herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to the preparation and administration of a product and, more particularly, to the injection of the same into a living organism, 10 for example, a human body.

Previously, various devices have been developed for the percutaneous delivery of medications into living organisms including syringes in which a liquid is delivered from a chamber using pressure asserted by a manual plunger through a needle inserted under the skin.

15 Additionally, it is well known in the art that the storage life of certain injectable substances such as glucagon, used to dissolve blood clots, is increased when the substance is stored in a powdered or lyophilized state, for example. These lyophilized substances (i.e., drugs or compounds) are presently used for injection of materials that would otherwise be unstable. Lyophilization, for example, is the rapid 20 freezing of a material at a very low temperature followed by rapid dehydration by sublimation in a high vacuum. The resulting lyophilized compound is typically stored in a glass vial or cartridge which is closed by a cap, such as a rubber stopper or septum.

It is necessary to reconstitute the powdered or solid material, such as a 25 lyophilized compound, prior to administration. This is accomplished by mixing the solid compound with a suitable diluent or liquid. Reconstitution typically involves the use of a syringe with a needle to withdraw the diluent from a separate vial and inject it into the vial containing the compound. The compound is then thoroughly mixed, typically by shaking the vial by hand, and a separate syringe with a needle 30 withdraws the desired amount to be injected into the patient. Because two separate containers are used, the person reconstituting the compound must be certain to mix the correct amounts such that a proper concentration of the mixture results. When a syringe is used to mix the diluent and drug, the exact volume of diluent to drug ratio

pressurizing systems may include, but are not limited to, a compressed air supply, a chemical gas generator, a collapsible volume supply, a bellow canister, a standard syringe or a cylinder, for example. The methods further include the step of delivering the pressurized diluent solution to the powdered drug vial. The next step 5 in the method includes the reconstitution of the drug to form a liquid drug by mixing the powdered drug with the diluent solution. The methods further include the steps of providing the liquid drug to an injector system or transferring the liquid drug to detachable delivery devices. The following step includes the injection of the liquid drug into the tissue of the patient or user. The methods further include the steps of 10 moving the injection needle from a delivery or injection position to a retracted or storage position once delivery is complete. It should be noted that, depending on the application or delivery of different medicaments, the features of the drug delivery systems may vary. For example, the pressurization level can vary depending upon the viscosity level of the medicament, and the needle type or length can vary 15 depending upon subcutaneous injection or intermuscular injection. For example, for subcutaneous injections, the needle length ranges from 5 to 12 mm while the needle length may vary up to about 3 cm for intermuscular injections.

The methods for delivering a liquid medicament to a patient include the steps of pressurizing the liquid drug solution in the vial with a pressurizing system. The 20 subsequent steps are similar to the steps described with respect to the methods for delivering a powdered medicament.

A preferred embodiment of the present invention features an injector system having an angled or u-shaped needle. Another preferred embodiment of the present invention features an injector system having a straight needle. Yet another preferred 25 embodiment of the present invention employs a transfer system for transferring the drug to delivery devices such as, for example, a standard syringe with a needle or a needleless pen injector. The devices receive the liquid drug from a container, such as a vial containing the liquid drug. The delivery devices subsequently deliver the medication to the user's tissue as described herein.

30 Another preferred embodiment of the present invention features a combination system having the ability to reconstitute drug into solution and subsequently inject it into a user. In accordance with this embodiment the

previously reconstituted material, can be inserted into the housing and simultaneously pressurized to the needed pressure to deliver the correct dose over a predetermined time period.

In a preferred embodiment of the system, the device is used with the 5 injectable fluid container being vertically oriented during injection. To reduce the risk of injecting any gas into the injection site, a gas impermeable membrane such as a hydrophilic membrane is disposed in the fluid path, which in a wetted state minimizes or preferably prevents gas flow while allowing liquid to flow through the membrane. The rigid containers need to be in a vertical orientation during 10 reconstitution for appropriate pressurization. In an embodiment including a cartridge having diluent and air, a vertical orientation is not required for reconstitution. According to a further aspect of the present invention, the axis of the injection needle is perpendicular to the longitudinal axis of the container with the injectable fluid. In a preferred embodiment, the containers containing a powdered or 15 lyophilized drug and diluent are inserted in the housing in the same direction along parallel axes. In another embodiment, the containers are inserted along a common axis or parallel axes in the opposite direction. The system can have housing apertures, ports, or openings that have a size compatible with standard vial and cartridge sizes such that existing vials and/or cartridges can be used. The container 20 contents do not have to be mixed until immediately prior to injection. Because the contents of the containers are only in contact with other sterile parts, sterility prior to and during the reconstitution process is maintained.

According to another aspect of the present invention a further improvement to reduce and preferably prevent the risk of injecting gas into the injection site, 25 includes the use of a drug which is gas impermeable once wetted. Further, since the gas impermeable membrane can sustain pressure, the delivery time for the liquid drugs is shortened as a higher driving force is generated using pressurization systems. By disposing such a membrane such as a hydrophilic membrane in the drug delivery path that is gas impermeable in a wetted state, gas needed to control 30 injection pressure and duration can be added in the system as the membrane checks the delivery of gas to the user. The container containing the fluid can be a changeable volume container which contains a controllable volume of a gas, for

use and that is readily transported by the user. In addition, the present invention is self-contained and maintains sterility throughout the reconstitution and injection of a fluid such as a lyophilized drug. It should be noted, the weight and volume of the system housing can vary depending upon the different embodiments and the volume 5 of drug being delivered to a user.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1F illustrate the operation of a preferred embodiment of a drug delivery device in accordance with the present invention.

Figures 2A and 2B illustrate cutaway views of the drug delivery device 10 shown in Figures 1A-1F, along line 2A, 2B - 2A, 2B in Figure 1F.

Figures 3A-3D illustrate the sectional views of the internal components of the drug delivery device of Figures 1A-1E and Figure 2 during administration of the reconstituted drug.

Figures 4A-4O illustrate the operation of a preferred embodiment of a drug 15 delivery device in accordance with the present invention.

Figures 5A-5C are perspective views of a preferred embodiment of a drug delivery device in accordance with the present invention.

Figures 6A-6C illustrate the operation of a drug delivery device substantially 20 similar to the device shown in Figures 5A-5C.

Figures 7A-7C are partial perspective views of the drug delivery device of 25 Figures 5A-5C and 6A-6C illustrating the injection of the drug.

Figures 8A-8F illustrate the operation of a drug delivery device substantially similar to the device shown in Figures 5A-5C.

Figures 9A-9F illustrate the operation of a preferred embodiment of a drug 25 delivery device in accordance with the present invention.

Figures 10A and 10B are graphical illustrations of the pressure, weight, and delivery characteristics of a preferred embodiment of the invention.

Figures 11A-11D illustrate cutaway views of an alternative embodiment including a drug container subassembly of the drug delivery device in accordance 30 with the present invention.

Figure 25 illustrates a cutaway view of an alternate embodiment of the drug transfer system in accordance with the present invention incorporating filling devices, for example a pen type pump to inject the liquid medicament.

Figures 26A-26D illustrate perspective views of a preferred embodiment of a drug transfer system in accordance with the present invention.

Figures 27A-27C illustrate cutaway views of a preferred embodiment of a drug delivery system in accordance with the present invention.

Figures 28A-28C illustrate cutaway views of the operation of a preferred embodiment of a drug delivery system in accordance with the present invention.

Figure 28D illustrates an enlarged cutaway view of a preferred embodiment of the spike which brings the liquid drug in communication with the delivery system in Figures 28A-28C.

Figures 29A and 29B illustrate partial cutaway views of a preferred embodiment of the drug transfer delivery system in accordance with the present invention.

Figures 30A and 30B are views showing the two piece construction of the manifold in accordance with the drug delivery system of the present invention.

Figures 31A-31G are perspective views of a preferred embodiment of a drug delivery system in accordance with the present invention.

Figures 32A - 32E are perspective views of another preferred embodiment of a drug delivery system in accordance with the present invention.

Figures 33A - 33I are cutaway views illustrating the interlocks built into the drug delivery system in accordance with the present invention.

Figures 34A - 34D are views of a preferred embodiment illustrating an end of delivery indicator of the drug delivery system in accordance with the present invention.

Figure 35 is a graphical illustration of a delivery profile of a preferred embodiment of the drug delivery system with no additional volume of air in the liquid vial in accordance with the present invention.

Figure 36 is a graphical illustration of the delivery duration and delivery pressure of a preferred embodiment of the drug delivery system in accordance with the present invention.

With reference to Figures 1A-1E, the general operation of a preferred embodiment of a drug delivery device 100 is illustrated. Figures 2A-2B, and 3A-3D provide sectional views of the same embodiment for clarity. As specifically illustrated in Figure 1A, drug delivery device 100 comprises a first member or 5 housing 304 and a pivotally connected second member or handle 106. The device 100 is used to mix, within a sterilized environment, a first liquid such as a diluent 166 (for example, a fluid such as sterilized water) with a second powdered drug such as a lyophilized drug or compound concentrate 164, e.g., interferon, and to inject the resulting reconstituted lyophilized drug into a living organism, which in the 10 preferred embodiment is a human being. Advantageously, the device 100 utilizes a standard vial or first storage container 102, which contains the lyophilized drug or compound 164, and a standard cartridge or second storage container 116, which contains the diluent 166. The device 100 may be formed from inexpensive materials, such as plastic or the like, such that it is economically feasible to dispose 15 of the device after a single injection.

In preparation for the administration of the drug, the user removes protective packaging which envelops the device 100. This packaging maintains sterility of the device 100 prior to use. In the preferred embodiment of the invention, cartridge 116 containing diluent 166 comes preassembled, being locked into the bottom of housing 20 304 by the arms 133 as shown in Figures 2A and 2B.

The sterility protector of the vial 102 is removed and then locked into the top of housing 304 as shown in Figure 2A with a needle 124 from the housing penetrating a stopper 112 of the vial. At this stage, vial 102 is filled with air at ambient pressure. The cartridge 116 is pushed upward, i.e., toward vial 102. The 25 cartridge 116 is punctured and the diluent 166 is delivered to the vial 102 as shown in part in Figure 1C. At this stage, as will be explained below, there is a fluid such as gas in vial 102 which is compressed by transfer of diluent 166 into vial 102. The user swirls the device 100 to ensure the lyophilized drug is appropriately reconstituted. The reconstituted lyophilized drug, or injectable fluid, is identified as 30 reference number 160.

Now, drug in solution with the diluent is ready for injection. The device 100 is pressed against the skin of the person to be injected with the vial 102 in a vertical

304 and is configured to pierce the rubber stopper 112 of vial 102 upon insertion of the vial into the locking position provided by arms 133. First needle 124 is fluidly connected to a first channel or tube 122 for receiving the diluent from cartridge 116 as illustrated in Figure 2B. Cartridge 116, similar to vial 102, preferably comprises 5 a standard cartridge (for example, a 2 milliliter cartridge with about 1 milliliter diluent) and includes a rubber stopper 118 which is pierced by a second needle 126, or other suitable means. Second needle 126 is fixedly mounted on an extending member or compression element 238 of housing 304 such that the cartridge is pierced upon insertion of the cartridge. First tube 122 is fluidly connected to the 10 second needle 126. Upon insertion of the cartridge 116, extending member 238 or compression element of housing 304 contacts and pushes rubber stopper 118 toward the bottom of cartridge 116. In this manner, the diluent 166 is forced up tube 122 into vial 102 to mix with the drug 164 contained therein. In the preferred embodiment of the present invention, cartridge 116 contains approximately 1 15 milliliter of diluent which is forced into vial 102, resulting in a pressure inside vial 102 of approximately 2.25 bars. This pressure can be adjusted, for example, by decreasing the amount of diluent or air in cartridge 116. A higher pressure inside vial 102 injects the reconstituted drug 160 more quickly.

Thus, a sterilized solution is provided wherein the diluent 166 is mixed with 20 the lyophilized drug 164 with minimal exposure to outside contaminants. It is preferable that vial 102 containing the reconstituted lyophilized drug 160 be visible during reconstitution and injection such that the user can properly visually verify that the lyophilized drug 160 is thoroughly mixed with diluent 166 and that the vial 102 is vertical during injection to ensure the compressed gas is not being injected 25 into the injection site.

Handle member 106 is pivotally connected to the housing 304 at a first end by a pivoting mechanism 110 which can include a rivet or other suitable means such that the handle member rotates in the direction of arrow 240. Handle member 106 includes biasing mechanism 108 which resiliently biases handle member such that 30 the end opposite the pivotally connected end is forced away from housing 304. Biasing mechanism 108 includes an extending member from handle member 106 which contacts housing 304, thereby providing a resilient biasing force away from

In Figure 3B, the device 100 is placed against the skin of the person being injected. The user presses handle member 106 toward the housing 304 in a direction shown by arrow 240A, thereby displacing injection needle 130 from the first position within the housing to a second position outside the housing such that the 5 needle penetrates the skin of the body being injected.

As shown in Figure 3C, continued pressure of the handle 106 towards the housing 304 causes the first bar member 140 to ride up the J-shaped slot 134. Simultaneously, second bar member 148, which includes a linear slot 244, is rotated such that first coupling device 142 rides up to the top of slot 244.

10 Figure 3D illustrates the continued pressing motion of the handle member 106 toward the housing 304. As the handle member 106 continues to pivot, the second bar member 148 forces third bar member 152 and hence third needle 128 upward such that third needle penetrates the rubber stopper 112 of vial 102. Because the reconstituted lyophilized drug 160 is under pressure, it is forced through 15 tube 120 and thus into the person being injected. At this point, biasing mechanism 108 is compressed. As the handle member 106 is released, biasing mechanism 108 forces the handle member away from the housing 304 as indicated by arrow 240B and thus withdraws injection needle within the housing. This is illustrated in Figure 3D. J-shaped slot 134 is beneficially provided with an end locking portion 146 20 which catches coupling device 142 such that the injection needle 130 is "locked" within the housing 304 after a single injection. Now, the device 100 can be safely discarded.

Figures 4A-4K illustrate a drug delivery device 100-1 in accordance with a preferred embodiment of the present invention wherein the same reference numbers 25 refer to the same or similar elements. More particularly, Figure 4A illustrates the device 100-1 which includes a housing 304-1 having a first port or opening 176 for receiving a diluent cartridge 116 and a second port or opening 262 for receiving vial 102. In this embodiment, it is preferred that cartridge 116 containing diluent 166 be preassembled such that the cartridge is partially penetrated by needle 126-1 and such 30 that the device 100-1 (without vial 102) is wrapped by a packaging material to maintain sterility prior to use. Again, it is preferable to use a standard 2 milliliter vial and cartridge that contains 1 milliliter of diluent. Thus, the user unwraps the

preferred that the injection needle 130-1 extend out of the housing 304-1 in the range of 5-12 millimeters. The injection needle 130-1 is in the range of a 24-28 gauge needle and is preferably a "U" type needle having a second end 172 configured to puncture sealing member 170. Sealing member 170, which can be any 5 puncturable material such as butyl rubber, sealingly maintains the liquid in the upper part of housing 304-1 prior to use.

It is preferable to prevent displacement of the injection needle 130 when the device 100-1 is not properly oriented, for example, upside down, in order to prevent the compressed gas in vial 102 from being injected. Also, it is preferable to lock the 10 injection needle 130-1 within the housing 304-1 after a single injection to reduce exposure to the contaminated needle. Additionally, it is preferable to only allow displacement of needle 130-1 after insertion of cartridge 116. Accordingly, a locking assembly 268A is provided to accomplish the foregoing.

The locking assembly 268A comprises member 268 as shown in Figure 4C 15 having a first end configured to be moved by pushing member 174 and a second end configured to displace a ball 270 or other appropriate movable locking device. With the pushing member 174 in the first position such that injection needle 130 is within the housing, groove 272 of the pushing member 174 aligns with groove 274 such that ball 270 can freely travel around the groove 274 of the pushing member. When 20 vial 102 is vertically oriented with the compressed gas above the liquid, thus being properly positioned for injection as shown in Figures 4B and 4C, ball 270 rests in the bottom of groove 274 allowing the pushing member 174 to displace the injection needle 130. If the vial 102 is not properly positioned (for example, the assembly 25 being upside down such that compressed gas would be injected, as shown in Figures 4E and 4F), the ball 270 is positioned within grooves 272 and 274 to prevent displacement of the pushing member 174.

The locking assembly 268A can be further configured to allow displacement of the pushing member 174 only after cartridge 116 is inserted. Figures 4G-4L illustrate this aspect of the invention. More particularly, Figure 4G is similar to 30 Figure 4C except cartridge 116 is shown outside of the housing 304-1. Figure 4H is a sectional view taken along line 4H-4H of Figure 4G and shows member 276 of the locking mechanism having a slotted portion 278 therein. Member 276 is slidable

cartridge 116. At this stage, the diluent from cartridge 116 has been transferred to vial 102, resulting in a pressurized liquid in the vial. The device 100-2 is vigorously shaken to ensure proper mixing of the reconstituted lyophilized drug. The device 100-2 is now ready for injection. It should be noted that the housing 304-2

5 advantageously includes a cutaway portion 254 which allows the user to visually inspect vial 102 to verify that the lyophilized drug 160 is thoroughly mixed with diluent 166 and to verify that vial 102 is vertically oriented during injection to ensure air is not being injected into the injection site.

Figures 6A-6C are plan views of a similar device 100-3 corresponding to

10 Figures 5A-5C, respectively. Accordingly, Figure 6A illustrates the cartridge 116 installed but not punctured by needle 126-3. Vial 102, containing the lyophilized drug 164, is also shown ready to be inserted into housing 304-3.

Figure 6B shows the inserted vial 102 which is punctured by needle 124-3. Vial 102 pushes first against surface 178-3 of puncturing device 182-3 and pushes

15 device 182-3 downward before being pierced by needle 124. Pushing puncturing device 182 downward sets a spring which (as will be explained in Figures 7A-7C) moves puncturing device upward such that needle 128-3 penetrates vial 102. Alternatively, the spring can be preloaded. As shown, needles 124-3 and 126-3 are fluidly connected by a manifold 127 comprising a channel 129 or tube. Upon

20 insertion of cartridge 116, the rubber stopper is first pierced by needle 126, and as cartridge 116 is further inserted into the circular opening 176-3 of housing 304-3, the rubber stopper 118 is forced to the bottom of cartridge 118, thereby forcing the diluent 166 through the manifold 127 into vial 102. This also compresses the gas that was heretofore contained in the vial 102 to a pressure sufficient for injection.

25 The resulting stage is shown in Figure 6C. The device 100-3 is preferably vigorously shaken to ensure proper mixing of the lyophilized drug 164. Now, the device 100-3 is ready to inject the reconstituted drug solution 160 contained in the vial 102.

Figures 7A-7C illustrate partial perspective views of the device 100-2, 100-3

30 shown in Figures 5A-5C and 6A-6C. More particularly, Figure 7A shows the pushing member 174-3 including an internal bore with member 252 slidably contained therein. Member 252 fixedly supports injection needle 130 which is in

forces the diluent under pressure into vial 102. This stage is shown in Figure 8B. Advantageously, the housing 304-4 includes a cutaway portion 400 such that vial 102 is substantially visible during reconstitution and injection. This allows the user to visually verify that the drug is properly reconstituted and that the vial 102 is 5 vertically oriented during injection with the compressed gas above the reconstituted drug.

Figure 8C is a rear view taken of Figure 8B and illustrates the injection of the reconstituted drug. More particularly, the pushing member or actuator 174-4 is pressed into housing 304-4 which forces injection needle 130-4 out of the housing 10 and into the person being injected. In the preferred embodiment, the injection needle extends out of the housing in the range of 5-12 millimeters. The reconstituted drug, in fluid communication with the vial 102, is transferred from the vial and into the person being injected. Figures 8D-8F are isometric views of the device 100-4 in the stages shown in Figures 8A-8C, respectively.

15 Figures 10A and 10B graphically illustrate system characteristics of a preferred embodiment of the drug delivery device. To provide effective delivery of a specified amount of fluid and minimize patient discomfort, the system requires a sufficient fluid pressure in the delivery vial that is manually actuated by the user within a short time period. Figure 10A shows the pressure (millibars) and weight 20 (grams) characteristics of the system during a delivery period of about 30 seconds for a delivery volume of about 1.6 milliliters. Figure 10B illustrates test results of the delivery of 1.6 milliliters into different animals using a single drug delivery device for the same time period.

Referring to Figures 11A-11D, cutaway views of a preferred embodiment of 25 a diluent container subassembly and a manifold, which may be used with the drug delivery devices or with an ordinary syringe or other drug delivery devices, are illustrated. The diluent container subassembly 300 includes a preassembled compression portion 310 which allows the user to hold the diluent container 312, which can be in the form of a compressible sealed bag, and insert it into a needle 30 314. The diluent container 312 contains about 1 milliliter diluent and a controlled volume of gas, such as air, for example, and upon insertion into housing 304-6, is pierced by the needle 314. During storage or shelf life, the diluent container 312 is

102. Thus, the diluent 166 is forced into vial 102 to mix with the lyophilized drug 164 contained therein. The entire assembly is preferably shaken to ensure the reconstituted drug 160 is properly mixed in preparation for injection. The vial 102 is vertically oriented during injection to ensure air is not being injected into the 5 injection site.

Referring to Figure 11C, the injector needle 130-6 is shown in a first position within the housing 304-6. As described hereinbefore, the injection needle 130-6 is in the range of a 24-28 gauge needle and is preferably a "U" shaped needle having a second end 172-6 configured to puncture sealing member 170-6. An area 171 is 10 located adjacent to the sealing member 170-6 and is in communication with the channel 331 as shown in 11B.

When the user compresses the button 305, it causes the needle 130-6 to penetrate the skin and the second end 172 to penetrate the sealing member 170. The drug and diluent solution will flow from the needle 332, through the channel 331, 15 and area 171 and to the user via the injector needle 130-6. As the user compresses the button 305, which is spring loaded by spring 306, a pair of mating pawls 307, 308 fit together and prevent the button from being pulled out and the reuse of the device as shown in Figure 11C.

Figures 12A-12B illustrate perspective views of a preferred embodiment of 20 the diluent container subassembly 300 and provide further details of the components of the compression portion 310. The cylindrical drum 324 is slotted such that the diluent container can be inserted therein. The cylindrical drum 322 serves as a backing drum. Thus, the diluent container 312 is typically inserted between the cylindrical drum 324 and the backing drum 322. The drum apparatus 322, 324 25 moves in a rack and pinion gear apparatus 340. An end of travel position 342 in the rack and pinion gear apparatus 340 constrains the movement of the cylindrical drum 324 at its end of movement position. This end of travel position correlates with the end of the wrapping of the diluent container 312 around the cylindrical drum and maximum compression of the contents of the container. A flange 344 can be used to 30 hold the diluent container 312 at the bottom of the subassembly 300. The diluent container 312 can be sealed by means of heat welding techniques or ultra sonic techniques to the flange 344 after it has been filled with the diluent. The

With the device 100-7 properly held by the user such that vial 102 is vertically oriented, the user presses pushing member 353 such that the injection needle 351 first extends out of the housing 304-7, thus penetrating the skin of the person being injected. Continued pressing of the pushing member 353 causes the 5 second end 355 of injection needle 351 to puncture sealing member 357, thereby allowing the pressurized reconstituted drug 166 to travel from vial 102 into the person being injected. It may take in the range of 10-30 seconds to deliver the injection fluid. The pressing motion compresses spring 359 such that upon release of pushing member 353, the member returns to the original position, i.e., the needle 10 is withdrawn within the housing 304 and locked therein.

Referring to Figure 14, a cutaway view illustrates a manifold of another preferred embodiment of the drug delivery device 100-8 in accordance with the present invention. The manifold 350 has two needles 352, 354 for the purpose of piercing vial 102 and diluent container 312, respectively. A flange, substantially 15 similar to the flange 127 shown in Figure 6B, holds the septum or stopper 313 in place in the container 312. An extending member or communication chamber 356 which is in fluid communication with the needles 352, 354, has a membrane such as a hydrophilic membrane or barrier 360 disposed therein. It should be noted that the hydrophilic membrane needs to be wetted before it functions to minimize or 20 preferably prevent the flow of gas into a user's tissue. The hydrophilic membrane allows gas, for example, air to pass freely till it comes in contact with liquid and gets wet. Thus, when wet, no air such as the controlled volume of air in the diluent container 312 can pass through the hydrophilic membrane, preventing air from entering the user's tissue. The presence of the hydrophilic membrane prevents risks 25 caused by any wrong use of the device 100-8 by the user such as incorrect positioning of vials or containers.

Referring to Figures 15A-15B, cutaway views illustrate another preferred embodiment of a manifold of the drug delivery device in accordance with the present invention. The needle 352 pierces the vial 102 while needle 354 pierces the 30 diluent container 312. The needle 354 and channel 352 on spike 352A are in fluid communication. Diluent 166 moves from the diluent container 312 into vial 102, thus mixing with the lyophilized drug to result in a reconstituted drug. A channel

The device 236 includes first opening 161 for receiving vial 102 and a manifold 370 including member 372 sealingly engaged with the first opening 161. Member 372 fixedly supports needle 374 and is supported by a collapsible volume, such as bellows 378, or any other device capable of injecting a fluid such as a gas upon being compressed. A check valve 380 ensures that the flow from the bellows is unidirectional, that is, the drug under pressure can not enter the bellows 378. The check valve 380 comprises a tubular member 381 adapted to deliver gas, for example air, to the vial 102. Air is moved out of the bellows and into the tubular member 332 by compressing, the bellows 378. The check valve 380 allows the flow of air out of the bellows 378 and into the vial but disallows the reverse flow of air from the vial into the bellows. Air from the bellows 378 is forced up through needle 374 and into vial 102 applying pressure to the contents of the vial 102. The liquid drug 160 is under pressure and is injected into the user directly from the vial 102. The injection process is the same as discussed earlier with respect to embodiments in Figures 13 - 15, in that the use of a U-shaped needle assembly is compressed into the skin to activate injection. As discussed earlier, due to the nature of the hydrophilic material, a hydrophilic membrane 360 in the drug delivery path minimizes and preferably prevents gas from being injected into the user.

Referring to Figures 17A-17C, cutaway views illustrate an alternate embodiment of the drug delivery device 100 in accordance with the present invention. The diluent container comprises a syringe 390. When pressure is applied to a plunger shaft 392, the diluent 166 is forced out of the syringe 390 through the channel 398 and into the contents of vial 102 via the needles 394, 396 which are in fluid communication with each other through the member 398. Thus, the diluent 166 is provided to vial 102 under pressure and is mixed with the reconstituted drug to result in a reconstituted drug solution ready for injection or delivery under pressure to a patient. The drug solution is delivered to a user using a u-shaped needle assembly as disclosed with respect to Figures 13A - 13B, 14, and 15A and 15B. This syringe embodiment facilitates the use of a standard prefilled container or cartridge containing only a diluent. The device is flexible and does not require special means or training.

Figure 9E. The pressing of the pushing member 226 into the housing 304-5 compresses a spring such that upon release of pushing member 226, the member returns to the original position, i.e., the injection needle 130-5 is in the first position within the housing 304-5 as shown in Figure 9F. This embodiment may be further 5 provided with a locking mechanism similar to that disclosed in Figures 4A-4K. With the injection needle locked within the housing 304-5, the device 236 may be safely discarded.

Further, Figures 18A-18C illustrate an injection device in accordance with an alternate preferred embodiment of the present invention. More particularly, the drug 10 delivery device 400 includes a straight needle 402 having a lancet 404 disposed on a first end. A cavity 405 in the septum 406 contains a liquid drug under pressure. The straight needle 402 includes a side hole 407 disposed on the shaft. The second end 408 of the straight needle is blocked. In operation, as shown in Figures 18A, 18A-1, 18B and 18B-1, when the member 410 is moved forward toward the housing 412, 15 the injection needle 402 is displaced from a first position in the housing 412 to a second position outside the housing such that the needle 402 penetrates the skin of the user. After the lancet 404 penetrates the user's tissue, continued pressing motion of the member 410 toward the housing causes the side hole 407 to be in fluid communication with the cavity 405 of the septum 406 creating a path for the drug 20 under pressure to flow into the user's tissue. The straight needle punctures the septum 406 at two locations. As shown in Figure 18C, as the member 410 is released, the injection needle is withdrawn within the housing 412.

More particularly, referring to Figure 18A-1, a 3 part ring structure including member 414, latch 416, gap 418 and spring 419, as shown in Figure 18A provide an 25 interlocking system. This safety mechanism which includes the members 410, 414, latch 416, gap 418 and spring 419 provides an interlock to ensure against reuse of the drug delivery device 300 and exposure of needle 402 after the first use. Once the member 410 is compressed the mating ridges 413A and 413B come together. The ridges are angled on one side to allow ridge 413B to pass under 413A when member 30 410 is depressed against the housing 412. The ridges are pressed together when the force of the spring 419 moves member 410 away from the housing 412. Because the ridges interface at a right angle to the direction of movement of the member 410

channel 453. Air is released from the compressed air canister 426 and is introduced into the diluent vial 422, which in turn forces the diluent solution 434 to move into the drug vial 420 via channel 455. After reconstitution is completed, the liquid drug is ready to be transferred. The concentration of the reconstituted drug can be
5 controlled in this and other embodiments by changing the quantity of diluent transferred to reconstitute the drug. A hydrophilic membrane 436 in the drug delivery path minimizes and preferably prevents gas from being transferred to the drug delivery device.

Figure 19C shows a chemical gas generator 428 as the air source used in this
10 particular embodiment to deliver the diluent 434 under pressure to the lyophilized drug vial. The chemical gas generator 428 includes a chemical compartment 456 which typically contains two materials 458, 460. The two materials 458, 460 can be two liquids or a liquid and a solid palette 460 that are separated during shelf life. It should be noted that the materials used in the chemical compartment 456 and the
15 reaction that ensues during the mixing of the materials are safe and biocompatible. Pushing a member 462, in the chemical compartment 456 results in tearing of a seal 464, for example, aluminum foil, which separates the two materials 458, 460 during shelf life. The two materials are then in fluid communication and react to produce a gas such as, for example, carbon dioxide. The chemical gas generator 428 also
20 includes a gas compartment 466 which is typically an air reservoir having a flexible enclosure 468. The carbon dioxide produced in the chemical compartment 456 due to the reactions enters the gas compartment 466 and is accommodated in the flexible layers 470, 472 that form the gas compartment. The movement of the flexible layers 470, 472 force the air or carbon dioxide into the diluent vial 422 through the
25 air pathway 423. It should be noted that the gas compartment 466 has a double layer 470, 472 comprising the flexible containment area. The two layers 470, 472 provide for safety as if the air or gas generated as a result of the reaction in the chemical compartment does leak, it can be accommodated between the flexible enclosure 468 of the gas compartment 466. Further, the gas compartment 466 is vented using a gas
30 leakage pathway or vent port 474. The air that is released from the chemical gas generator 428 enters the diluent vial 422 via the channel 423 which in turn forces the diluent solution 434 to move into the drug vial 420 via the channel 425. After

Referring to Figure 19F, the air source used in this particular embodiment to deliver the diluent under pressure is cylinder 490. This embodiment is similar to the embodiment containing a standard syringe as described with respect to Figure 19D. The plunger 492 is depressed to compress the air in the cylinder 490. The air is 5 driven into the diluent vial 422 through channel 494 which brings the cylinder and the diluent vial in fluid communication. The pressurized diluent in diluent vial 422 then moves into the vial 420 and mixed with the drug. The pressurized drug solution is then ready to be delivered. This can either comprise delivery to a drug delivery device as described with respect to the embodiment of Figure 19A or 10 injected as shown in the present embodiment having a straight needle assembly as shown and described in Figure 18.

Referring to Figures 20A-20C, an alternate embodiment of the drug delivery system 498 in accordance with the present invention includes standard vial 500 containing a liquid drug 502. A volume of gas, for example air, contained in an air 15 chamber 504 is introduced in the standard liquid drug vial 500, creating air pressure above the liquid drug which allows for delivery of a liquid drug under pressure. The usage is position dependent, that is the delivery of the liquid drug, is performed with the standard vial 500 in a vertical position. In addition, a hydrophilic membrane minimizes or preferably prevents the introduction of the extra volume of air into the 20 user's tissue.

In use, as shown in Figure 20A, the standard vial 500 containing the liquid medicament 502 is inserted into the drug delivery device 498 in accordance with the present invention. An air chamber 504 is provided which upon insertion of the drug vial 500 and the puncturing of the seal 506 of the vial, is in fluid communication 25 with the drug vial. Once inserted, the lip 505A of a standard vial 500 is locked into position by means of a pair of arms 505 having ridges 507 projecting inwardly therefrom. The injector system is the straight needle 402 embodiment as disclosed in Figures 18A-18C. Once the air from the air chamber is introduced into the standard drug vial 500 the liquid drug is pressurized and is ready to be injected using 30 the injector system described with respect to Figures 18A-18C. After injection into the user's tissue, the needle is retracted automatically. The drug delivery device 498 is then disposed.

syringe and manifold is included in the embodiment containing the syringe. The drug delivery system of the present invention is used to deliver an accurate volume of a drug solution. The predetermined volume can be delivered using different methodologies. A first embodiment controls the dose by changing the 5 height of the outlet spike 535 in the liquid drug vial 537 as shown in Figures 23A, i.e. the higher the spike, the lesser is the amount of drug transferred out of the vial 537. The spike is adjusted by means of threads 539 upon which the spike rotates or upon which it sealably slides. This can be used for to transfer or to inject the drug solution. Another preferred embodiment which increases the accuracy of the 10 volume of drug delivered uses the residual drug volume as a parameter to indicate the volume delivered. One way of controlling delivered drug solution volume is to use the assembly shown in Figure 23B. After the drug is pushed in solution in vial 102 the solution may be pulled into cavity 541 by piston 555. The cavity 541 has indications thereon to aid the user in determining the proper volume. At the desired 15 level, the piston is stopped. The drug solution is then transferred from the cavity 541 either via a needle into a user or into a drug delivery device. Yet another embodiment to provide an accurate volume of drug is disclosed with respect to Figures 24A-24C and Figure 25. The reconstitution system having the vial containing the reconstituted drug is essentially used as a filling station by a 20 detachable delivery device, for example, a standard syringe or a pen type pump.

Referring to Figures 24A-24C a position independent injector system 540 is illustrated. The drug 545 is reconstituted similar to the description provided with respect to earlier systems such as illustrated in Figure 19F. After the drug has been reconstituted it can be aspirated by a conventional standard syringe 542 for the exact 25 dose required. The accuracy using this method is about +/- 5%. The fluid level in the cavity 550 is controlled by adjusting the pressure and geometry of the device 540. The needle is held in place by the elastomeric septum or stopper 552. In use, once the reconstituted drug is aspirated into the syringe 542 by moving plunger 548 which moves the stopper 554 upwards allowing the syringe 542 to be filled with the 30 liquid drug, the syringe 542 is removed from the drug delivery device 540. The accuracy of the volume of the liquid drug delivered is determined by the scale on the syringe. The user then injects the drug and disposes of the syringe by one of

via an extension 606. The liquid drug flows out of the vial 602 through spike 608 and through the tubing 610 into the needle 616 which is received into the drug delivery device 604.

Referring to Figure 27B, the drug delivery device 604 is attached to the transfer system 600. The filling process continues until the entire drug level reaches the outlet 604A (shown in phantom in Figure 26B) of the device 604. At this point the filling process is completed. It should be noted that during the filling process, if the user stops pushing the vial 602 into the transfer system 600 the drug may drain into the cylinder 614. This is prevented by getting the friction forces higher than the impedance of the tubing 610 to the drug flow. In the alternative, it is also possible to dispose a one-way valve at the end of the tubing 610. Once the drug delivery device 604 is filled with a liquid drug, it is disconnected from the transfer system 600. Any residual drug in the system 600 can stay protected, and the needle 616 is retracted and as described earlier with respect to the needle locking mechanisms is secured in the cover 606, and cannot be reexposed to cause harm or injury.

Figures 28A-28C are cutaway views of the operation of another preferred embodiment of a drug delivery system 630, in particular of a position independent injection system in accordance with the present invention. In this embodiment, the injection system 630 is position independent, that is the injector is not required to be in a vertical position during the injection process. Referring to 28A, the drug delivery system 630 includes a vial 632 containing the liquid drug 634. The liquid drug 634 flows through the spike 636 along a tube 644A into a cavity 652. The spike includes two paths, one path 642 for delivering pressurized air into vial 632 from chamber 641 and another path 644 to deliver the liquid drug to the user via a needle 664. The liquid drug exits from the path 644 and travels along tube 644A disposed at the bottom of the spike. A one-way valve 638 insures the unidirectional flow of the liquid drug 634 into the cavity 652A. Spring 640 holds piston 656 within the cavity 652. A floating piston 650 moves in the cavity 652. A seal 654 is included in the floating piston. Member 660 rests atop a needle assembly 664A. Member 660 is hingedly connected to member 662. Member 662 has a finger 662A.

mechanisms may be included in the injector system to result in a position independent injector.

Referring to Figure 28D, a cutaway view of a spike 636 which brings the liquid drug 634 in fluid communication with the injector system is illustrated. The 5 spike 636 penetrates the septum 639 of the vial 632 when the vial is inserted into the cavity 640. The spike functions as a piston 641A and is sealably and slidably movable by means of the seal 641B within the interior walls of the chamber 641. As described hereinabove, the spike also consists of two paths, an air inlet 642 and a drug outlet 644. Once the vial 632 is inserted, pressurized air enters the vial 632 10 from an air chamber 641 and forces the liquid drug 634 via a flexible tube 644A to the injector system. The filling process for the injector system in a preferred embodiment is preferably done under a maximum pressure gradient of 0.3 bar. This includes a margin for example, priming at an altitude of 5,500 feet and is the maximum expected back pressure.

15 Figures 29A and 29B illustrate partial cutaway views of another preferred embodiment of the drug transfer system 670 in accordance with the present invention.

The drug vial 672 containing the liquid drug 674 is inserted into a cavity 676. A spike 678 provides air into the liquid drug vial 672 for pressurization of the drug 674 20 and additionally the spike provides for an outlet for the liquid drug to be delivered to a drug delivery system 680. The drug transfer system 670 is in fluid communication with the liquid drug vial 672 through a flexible tubing 682 and a needle 684. A hydrophobic membrane 686 is disposed in the flexible tubing 682 to prevent the transfer of air into the drug delivery system. This hydrophobic membrane 686 25 prevents back flow. The air to pressurize the liquid drug 674 is provided by air in the reservoir 675. Further, a latch mechanism 688 secures the vial 672 to the detachable delivery system 680 during a filling process.

Referring to Figure 29A -1, an enlarged view of the interface between the drug transfer system 670 and the detachable drug delivery device 680 is illustrated. 30 A hydrophobic membrane 692 is disposed at the interface for blocking the flow of the drug once the drug delivery device 680 is filled. An elastomeric cover 694 is

depression of the knob mechanism and subsequent injection is similar to that described earlier with regard to either the straight needle assembly shown in Figure 18 or the U-shaped needle shown in Figures 11, 13 through 17.

Referring to Figures 31F and 31G, two preferred embodiments 711, 713 which provide a visual indication of device orientation are illustrated. The vertical indicators 711, 713 are shown as being disposed on the top of the plunger 708, however their location can vary to provide appropriate visual indication. In the first embodiment of the vertical indicator 711, a metal ball 714 rests upon a curved surface having visual indicators or scale 712 thereon. The ball 714 is enclosed within a clear casing 712A. The positioning of the ball 714 in the middle of the scale is an indication of vertical orientation. In the second embodiment 713 of the vertical indicator, an air bubble 716 disposed in a liquid 718 enclosed within a clear housing 718A is used as the visual indicator of orientation with respect to the scale 719. The positioning of the air bubble 716 in the middle of the scale is an indication of vertical orientation.

Referring to Figures 32A-32E, perspective views illustrate a further alternate embodiment of the drug delivery system 720 in particular a reconstitution and injection system, in accordance with the present invention. In this embodiment the reconstitution of the drug occurs by the mixing of the diluent solution with the drug. A separate pressurization system for the diluent is not required for this particular embodiment and can only be used with low viscosity drugs. In use, the knob 730 is moved in a counter clockwise direction to begin the reconstitution process of the drug which opens a pathway connecting the diluent with the drug. The knob 730 is turned from a non-use position (as indicated when notches A and B align) to a ready to use position as indicated with the alignment of notches B and C. At this point, the knob 730 may be depressed and the solution injected. The internal pressure of the diluent vial and gravity cause the diluent to transfer to the vial containing the drug. Further movement of the knob or dial 730 activates an injection needle which interfaces with the user's tissue to deliver the reconstituted drug. Again, the injection assembly is similar to the embodiments shown in Figures 11, 13-17.

Referring to Figures 33A - 33I, cutaway views of preferred embodiments of the drug delivery system emphasizing the interlocks disposed to provide for a safe

Referring to Figures 33F and 33G, during the injection process different interlock elements insure the safe use of the drug delivery system. As the pushing member 776 is depressed, which is only allowed if the drug delivery system 750 is in a vertical orientation, the horns 778 spread the latch 780 which allows the 5 member 770 to press the ball 772 in the upward direction. Note the pushing member 776 is already pushed to expose the needle 782.

Referring to Figures 33H and 33I, the interlocks during the phase of disposing of the drug delivery device which follows the injection phase are illustrated. The pushing member 776 is released by the action of the spring 777 10 pushing the member 776. Since the movement of the ball 772 was limited by the body of the member 776, with the release of the member 776, the ball 772 can now move back into the groove 774 as it is assisted by the pressure applied by the rear shell latch 780. This locks the pushing member 776 into position thereby preventing further use of the drug delivery device 750.

15 Referring to Figures 34A through 34D, a preferred embodiment of the drug delivery device having an end of delivery indicator is illustrated. As discussed previously with respect to preferred embodiments of the drug delivery system of the present invention, the drug delivery system is activated by pressurized gas, for example, air. The air forces the drug to the injection site by pressurizing the drug. 20 A hydrophilic membrane minimizes and preferably prevents the passage of air into the user's body. The hydrophilic membrane is disposed in the drug path to the user's tissue. Once wetted, the hydrophilic membrane allows liquid drug to proceed into the user's tissue and stops the passage of air into the user's tissue. In order to insure the effectiveness of the membrane, the hydrophilic membrane has to become 25 wetted. To enhance the effectiveness of the drug delivery device, a hydrophobic membrane is also positioned in the drug path. Referring to the figures 34A and 34B, an inlet 800 which provides the liquid drug 802 into a cavity 803 has both a hydrophobic membrane 806 and a hydrophilic membrane 810 disposed therein. The hydrophobic membrane 806 allows air to pass, but stops liquids. On the other 30 side of the cavity 803 the hydrophilic membrane 810 allows liquid drug to pass while stopping the flow of gas. At one end of the hydrophobic membrane 806 a flexible elastomeric diaphragm is disposed that acts as an indicator once filled with

example, air into the user's tissue. The test results prove membrane safety to insure that the membrane can withstand the pressures in the order of 2,700 millibars for a time duration of about six minutes.

Figure 39 graphically illustrates the performance of a drug delivery device in accordance with the present invention. Three delivery profiles 840, 842, 844 (in ml) vs. time (in seconds) are illustrated for a reconstituted lyophilized drug delivery system. The system includes a 0.45 micron pore size hydrophilic membrane to minimize or preferably prevent the flow of gas into the user's tissue. This particular pore size of the membrane provides an adequate particle filter and also allows the shortest time to deliver the drug to the user's tissue.

Figure 40 is a flow chart that describes the methods for delivery of a lyophilized drug in accordance with the present invention. The methods include the step 899 of inserting the drug and diluent containers into the drug delivery device. Further per step 900, the method includes activating a pressurized air source which in turn is followed by the step 902 of pressurizing a diluent solution in a diluent vial. As discussed with respect to Figures 19A-19F, the pressurizing can be provided by subsystems which include but are not limited to a compressed air supply, a chemical gas generator, a collapsible volume air supply, a standard syringe or cylinder.

The methods further include the step 904 of delivering the pressurized diluent solution to the lyophilized drug vial. The lyophilized drug is reconstituted per step 906 as a result of the mixing of the diluent with the lyophilized drug. The methods further include the step 908 of providing the liquid drug to an injector system or transferring the liquid drug to a detachable delivery device. The liquid drug is then injected into a user's tissue per step 910. The injection needle is then moved to a safe storage position per step 912.

Figure 41 is a flow chart that describes the methods for delivering a liquid medicament in accordance with the present invention. The methods include the step 913 of inserting a drug container such as a vial into the drug delivery system. Further, per step 914 the method includes activating a pressurized air source for low viscosity drugs. It should be noted that for drugs with a high level of viscosity no pressurization may be required. The method then includes the step 916 of pressurizing the standard drug vial. The pressurized liquid drug is transferred to a

anginal agents such as fluorouracil, bleomycin, and analogues thereof; anti-neoplastics such as fluorouracil, bleomycin, and analogues thereof; prostaglandins and analogues thereof; and chemotherapy agents such as vincristine, and analogues thereof, treatments for attention deficit disorder, methylphenidate, fluvoxamine, 5 bisoprolol, tacrolimus, sacrolimus and cyclosporin.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended 10 claims. For example, some of the features of the position independence can be used in connection with reconstitution combination systems, transfer systems or injection systems. Likewise interlock features may be used with any of the aforementioned systems.

7. The system of Claim 1 wherein the material is a drug that is transferred with a needle into tissue.
8. The system of Claim 1 wherein the material is a drug that is transferred to a drug delivery device.
- 5 9. The system of Claim 5 further comprising a sealing element in said second container that allows a fluid from second container to flow through said second penetrating member to said first container when an actuator moves the sealing element.
10. The system of Claim 9 wherein the actuator includes a pressure source.
- 10 11. The system of Claim 1 further comprising a support surface on the housing such that the first and second containers are received along axes extending orthogonal to the support surface.
12. The system of Claim 1 wherein the contents of the first container is a solid material.
- 15 13. The system of Claim 1 further comprising a metering element that controls a volume of the drug being transferred.
14. The system of Claim 13 wherein the metering element includes a penetrating member that extends an adjustable distance into the first container.
- 20 15. The system of Claim 1 further comprising a position indicator that indicates a position of the first container.
16. The system of Claim 1 further comprising a transfer indicator that indicates movement of the drug within the housing.

-51-

25. The method of Claim 21, further comprising providing a first contents that is a liquid drug.
26. The method of Claim 21 further comprising providing a first contents that is a powder.
- 5 27. The method of Claim 21 further comprising providing a first contents that is a lyophilized drug.
28. The method of Claim 21 wherein a user inserts the first container and the second container into the housing using one hand.
- 10 29. The method of Claim 21 further comprising providing a manifold in the housing in which the channel has been formed.
30. The method of Claim 29 further comprising providing a second channel in the manifold through which the solution is transferred from the first container.
- 15 31. The method of Claim 21 further comprising providing an interlock such that the first container must be inserted before the second container.
32. The method of Claim 21 further comprising providing a position indicator that indicates a position of the housing to a user.
33. The method of Claim 21 further comprising providing a transfer indicator that indicates a movement of the solution to a user.
- 20 34. The method of Claim 21 further comprising a membrane that prevents movement of a gas.
35. A drug transfer system comprising:

a port in said housing that receives a rigid container that contains an injectable drug;

5 a first penetrating member movable from a storage position in the housing to an injection position extending outside the housing through the aperture; and

a channel that brings said penetrating member into fluid communication with the first container.

42. The injection device of Claim 41 wherein the channel comprises a fluid pathway in a manifold, the manifold further comprising a second channel to transfer the injectable drug from the housing to the user.
- 10
43. The injection device of Claim 41 further comprising an actuator that displaces the penetrating member from the storage position to the injection position.
- 15
44. The injection device of Claim 43 wherein the actuator includes a plunger mechanism on a first housing surface that displaces said first penetrating member through the aperture on a second housing surface between the storage position and the injection system.
- 20
45. The device of Claim 41 further comprising a locking mechanism that prevents displacement of said first penetrating member to said injection position after injection.
- 25
46. The injection device of Claim 41 further comprising a biasing mechanism that resiliently biases the penetrating member in said storage position.
47. The injection device of Claim 41 further comprising a penetrating member retraction system that retracts said penetrating member into the housing after injection.

providing a housing having a first port that receives a first container of fluid;

inserting the first container in the housing;

pressurizing the fluid in the container; and

5 transferring the fluid from the first container through a channel in the housing.

56. The method of claim 55 further comprising the steps of:

providing a movable member slidably and sealingly positioned within the first port, the movable member fixedly supporting a first penetrating member in fluid communication with the container; and

collapsing a collapsible volume with the movable member upon insertion of the first container into the first port, the collapsible volume being in sealed communication with the first penetrating member to pressurize the container.

15 57. The method of claim 55 further comprising a second port in the housing that receives a second container that pressurizes the fluid in the first container as said second container contains a fluid to be transferred into the first container, further comprising the step of pressurizing the first container upon transfer of the fluid.

20 58. The method of claim 55 further comprising the step of penetrating the container with a first end of a penetrating member on the housing and then coming into fluid communication with the fluid.

59. The method of claim 55 further comprising providing a gas impermeable membrane along at least a portion of a fluid path in the housing.

25 60. The method of claim 55 further comprising providing a compressible volume, and compressing the volume to pressurize the container.

66. The device of claim 61 further comprising a locking mechanism that prevents movement of said injection penetrating member to the injection position when the first container is not vertically oriented.
67. The device of claim 63 wherein said actuator includes a handle member pivotally attached to said housing and a bar member connected to a slidable member, said slidable member supporting said first penetrating member and displaced by said handle for moving said first penetrating member between said storage and said injection position.
5
68. The device of claim 61 further comprising a mixing device that mixes said fluid with said material, said mixing device comprising:
 - a second penetrating member fixed to said housing and that penetrates said second container;
 - a third penetrating member fixed to said housing and that penetrates said first container; and
10
69. The device of claim 68 further comprising a sealing element in said second container that displaces the fluid from said second element container through said second penetrating member to said first container upon insertion of said second container into said second port such that the compression element moves the sealing element.
15
70. The device of claim 68 further comprising:
 - a fourth penetrating member positioned within said housing and that penetrates said first container; and
 - 20
 - 25
 - a second channel that fluidly connects said first and said fourth penetrating members.

80. The device of claim 61 wherein said first and second containers comprise vials having a two millimeter volume.
81. The device of claim 61 wherein said first penetrating member extends in the range of 5-12 millimeters out of said housing in said injection position for 5 subcutaneous injection.
82. The device of claim 61 wherein said first penetrating member extends up to about 3 cm out of said housing in said injection position for intermuscular injection.
83. The device of claim 61 wherein the solid compound is one of a powdered drug and lyophilized drug. 10
84. The device of claim 61 further comprising an interlocking mechanism that prevents insertion of said second container before insertion of said first container into the housing.
- 15 85. The device of claim 61 wherein the material for injection is a lyophilized drug.
86. A method of transferring a fluid comprising the steps of: providing a housing member having an aperture; providing a first port in said housing that receives a first container 20 that contains a solid compound for injection; inserting a first container in said housing; providing a second port in said housing that receives a second container that contains a fluid to be mixed with the solid compound to form a mixed fluid;
- 25 inserting a second container in said housing; providing a first channel in fluid communication between the first and second containers;

an actuator which causes the manifold to come into fluid communication with the injection penetrating member.

92. The device of claim 91 further comprising a locking mechanism that prevents displacement of said injection penetrating member to said second position after a single injection.
5
93. The device of claim 91 further comprising a biasing mechanism that resiliently biases said injection penetrating member in said first position.
94. The device of claim 91 further comprising a penetrating member retraction system that retracts said injection penetrating member into the housing after injection.
10
95. The device of claim 91 wherein said injection penetrating member extends outside of the housing to establish fluid communication with the first vial.
96. The device of claim 91 wherein said second drug component is transferred under pressure into the first vial upon insertion of the second vial into the second port.
15
97. The device of claim 91 wherein the first vial comprises glass which is visible during transferring of the second drug component and during injection.
98. The device of claim 91 wherein the injectable fluid in said first vial is pressurized to inject said injectable fluid.
- 20 99. The device of claim 91 wherein the first drug component is a lyophilized drug.
100. A method of transferring a fluid comprising the steps of:
providing a housing having an aperture;

104. The device of claim 102 further comprising a sealing member to maintain the injectable fluid in the fluid container in an upper end of the housing.
105. The device of claim 104 wherein the injection penetrating member includes a first end to pierce skin of the body being injected and a second end to pierce the sealing member after the first end has penetrated the skin.
5
106. The device of claim 101 further comprising an actuator that displaces the injection penetrating member between the storage position and the injection position.
107. A method of transferring a fluid comprising the steps of:
10 providing a housing having an aperture and a first port that receives a first container that contains an injectable fluid;
pressurizing the fluid in the container; and
actuating a valve to transfer the fluid through the aperture.
108. The method of claim 107 further comprising the steps of:
15 providing a movable member slidable and sealingly positioned within the first port, the movable member fixedly supporting a first member in fluid communication with the container; and
collapsing a collapsible volume with the movable member upon insertion of the first container into the first port, the collapsible volume being
20 in sealed communication with the aperture to pressurize the container.
109. The method of claim 107 further comprising a second port in the housing that receives a second container that contains a fluid to be transferred into the first container, further comprising the step of pressurizing the first container upon transfer of the fluid.
- 25 110. A liquid drug transfer system comprising:
a housing;

119. The liquid drug transfer system of Claim 110 wherein the delivery device comprises a pen injector.
120. The liquid drug transfer system of Claim 110 wherein the delivery device comprises a detachable housing having a needle having a storage position within the detachable housing and an operating position that extends through an aperture in the detachable housing.
5
121. The liquid drug transfer system of Claim 110 wherein the housing further comprises a manifold having a channel through which liquid is transferred from the container to the delivery device.
- 10 122. The liquid drug transfer system of Claim 110 further comprising a second port in the housing that receives a second container having a fluid therein.
123. The liquid drug transfer system of Claim 122 further comprising a manifold in the housing having a first channel that connects the second container with the container and a second channel that connects the container to the delivery device.
15
124. A method for transferring a liquid comprising:
inserting a container in a housing;
transferring a liquid in the container to a delivery device, the delivery device having a penetrating member; and
separating the delivery device from the housing.
20
125. The method of Claim 124 further comprising providing a delivery device including a syringe.
126. The method of Claim 124 further comprising providing an end of delivery indicator.

1/76

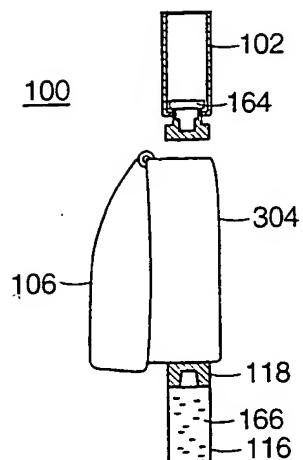


Figure 1A

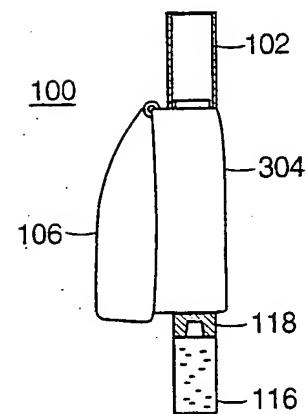


Figure 1B

3/76

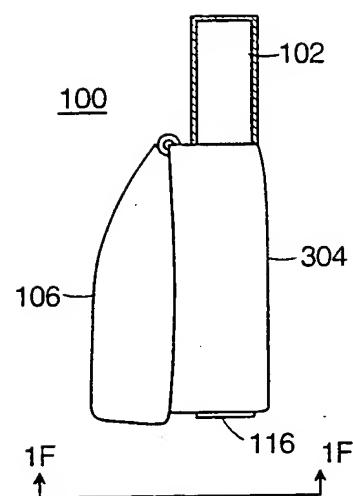


Figure 1E

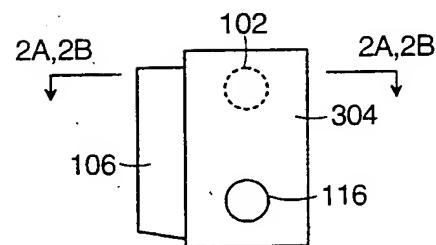


Figure 1F

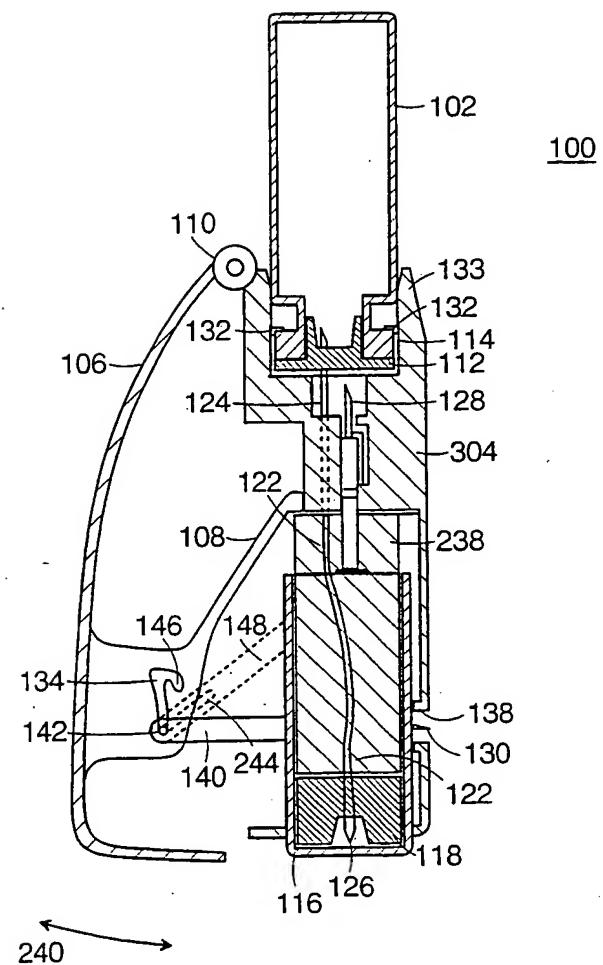


Figure 2B

7/76

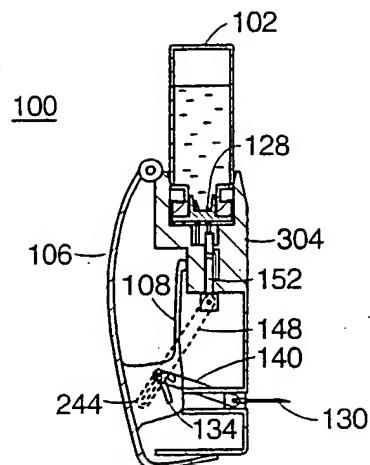


Figure 3C

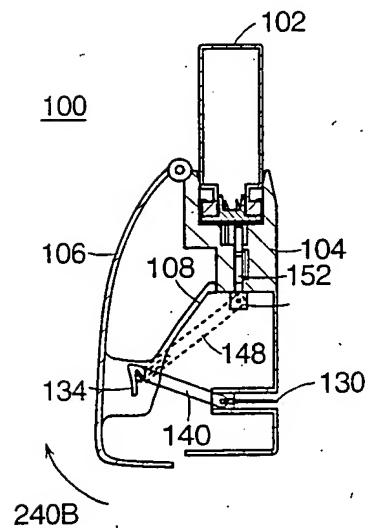


Figure 3D

9/76

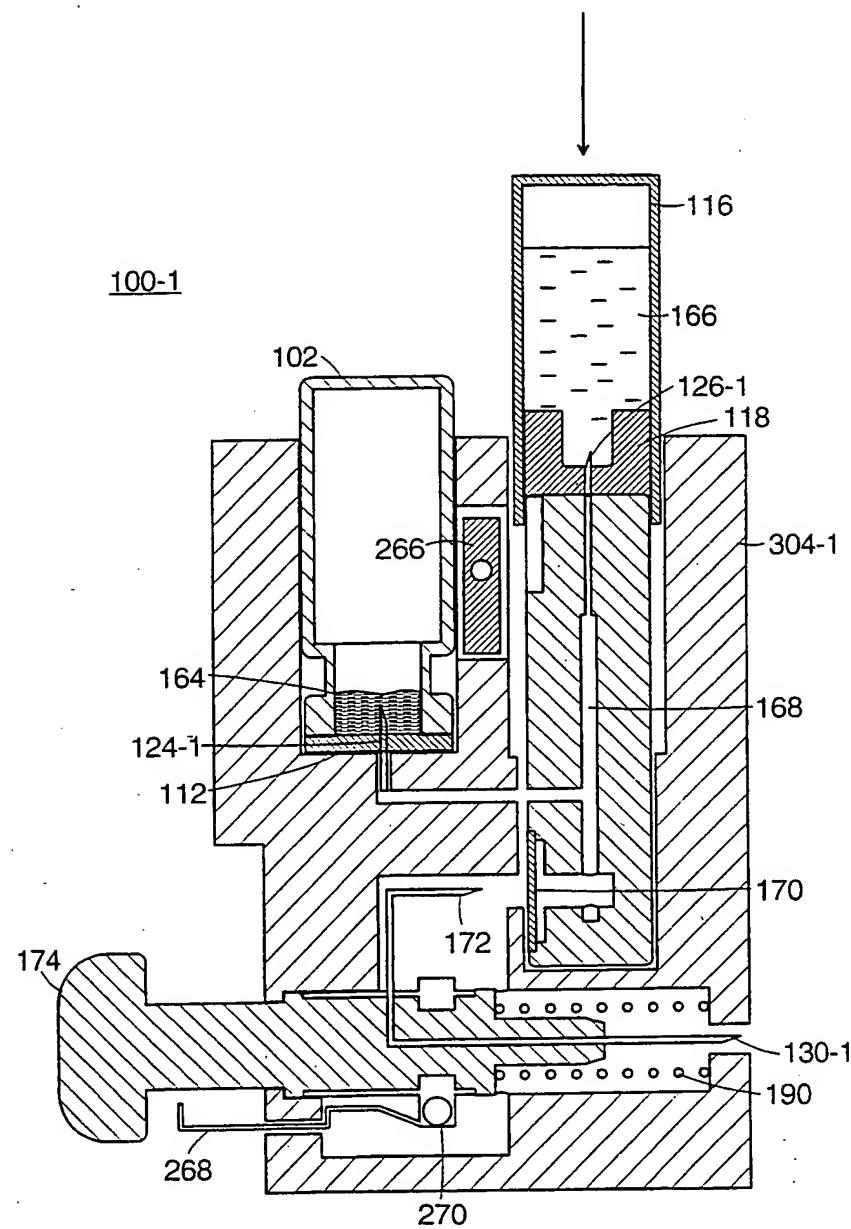


Figure 4B

11/76

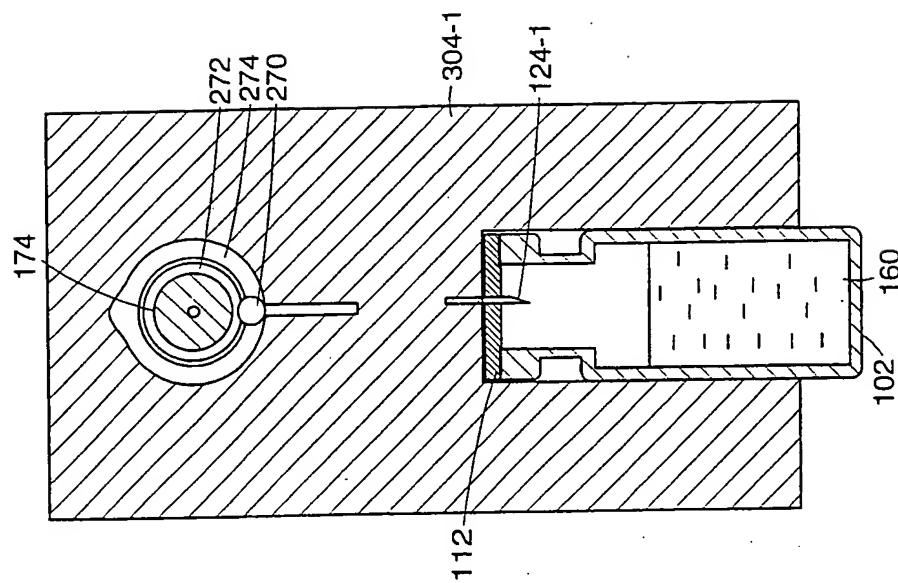


Figure 4F

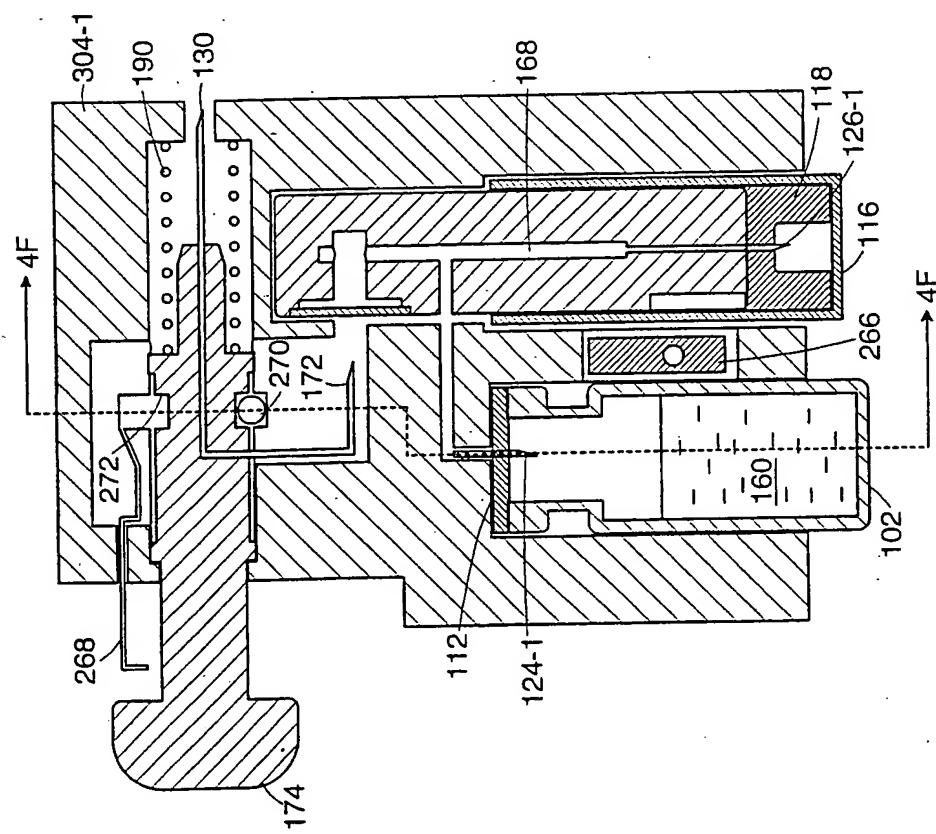


Figure 4E

13/76

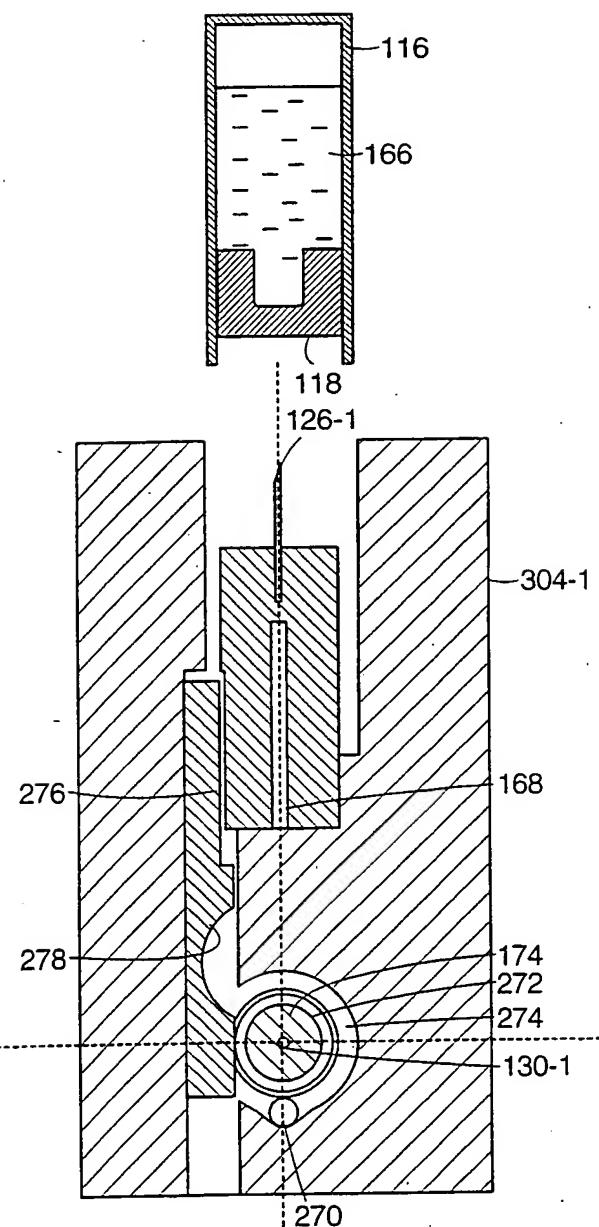


Figure 4H

15/76

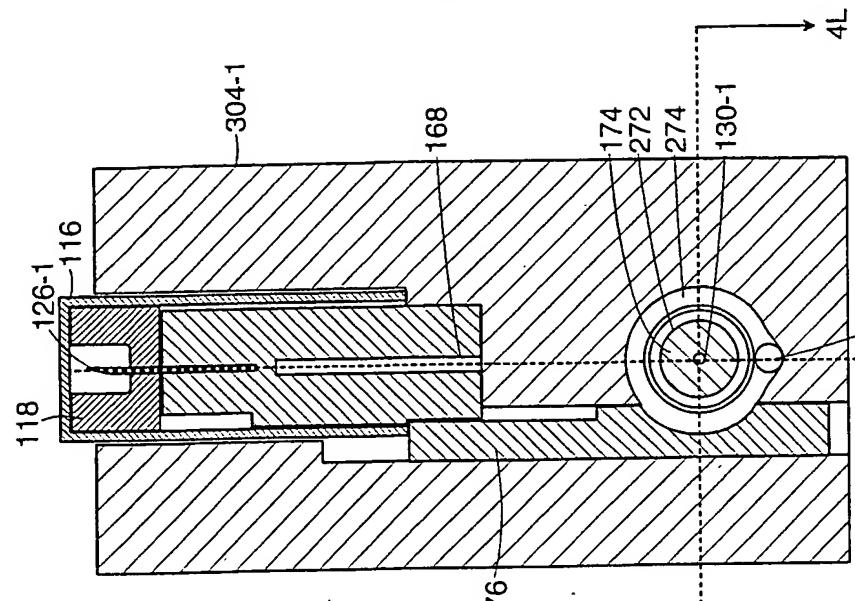


Figure 4K

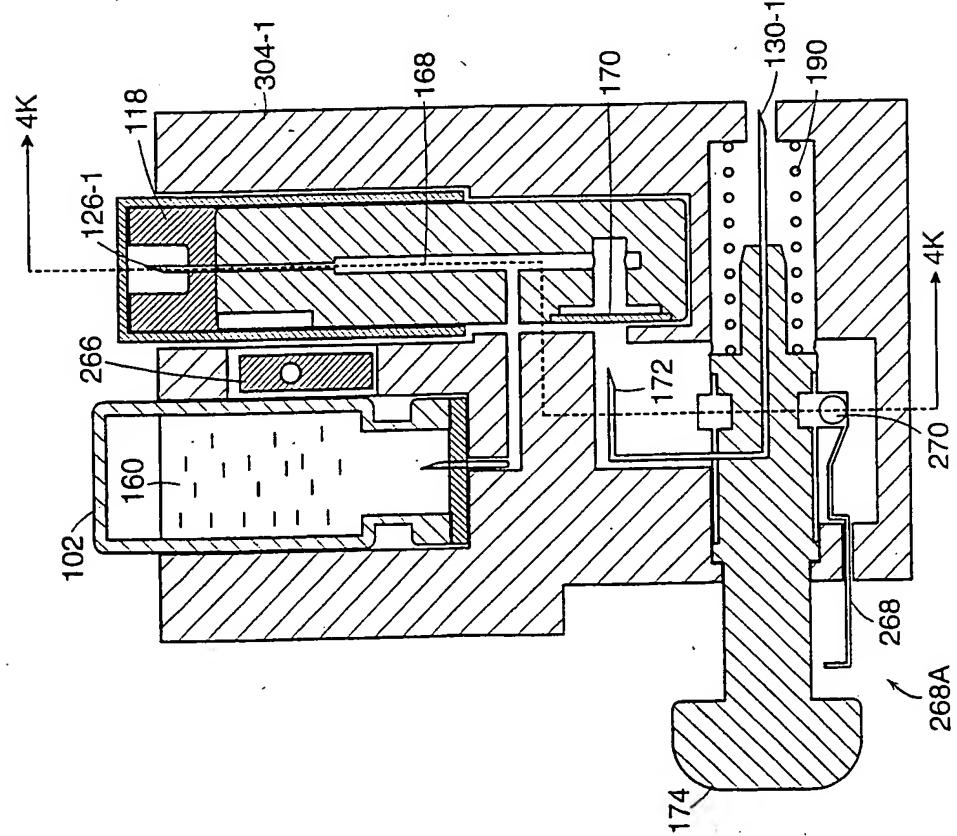


Figure 4J

17/76

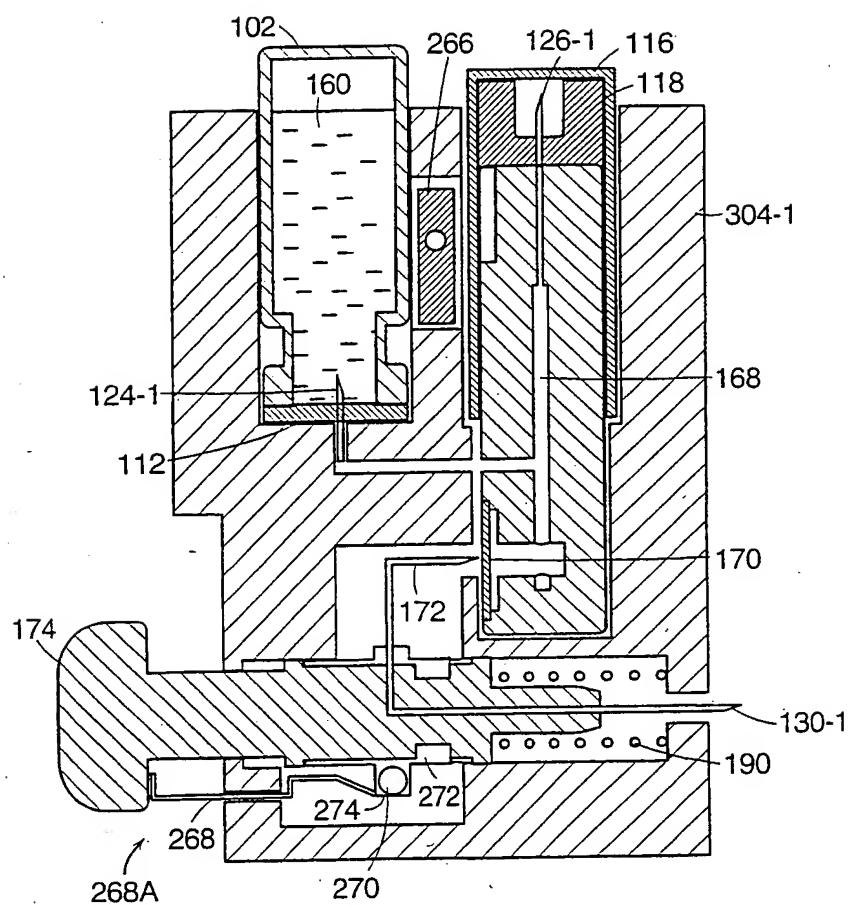


Figure 4M

19/76

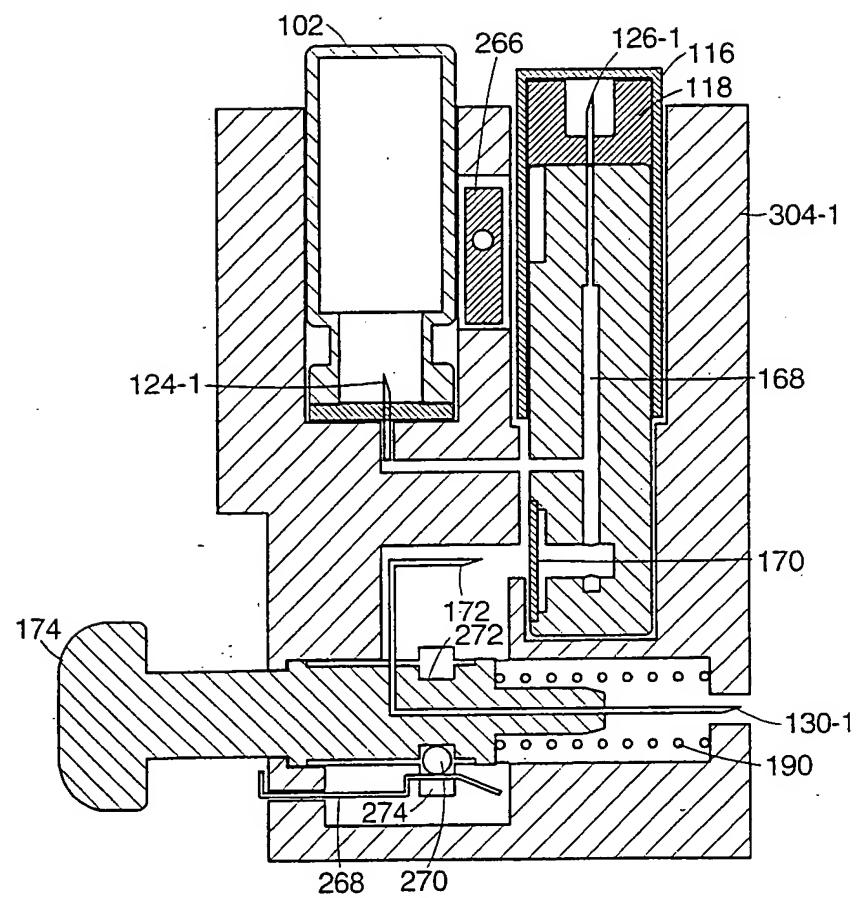


Figure 4O

21/76

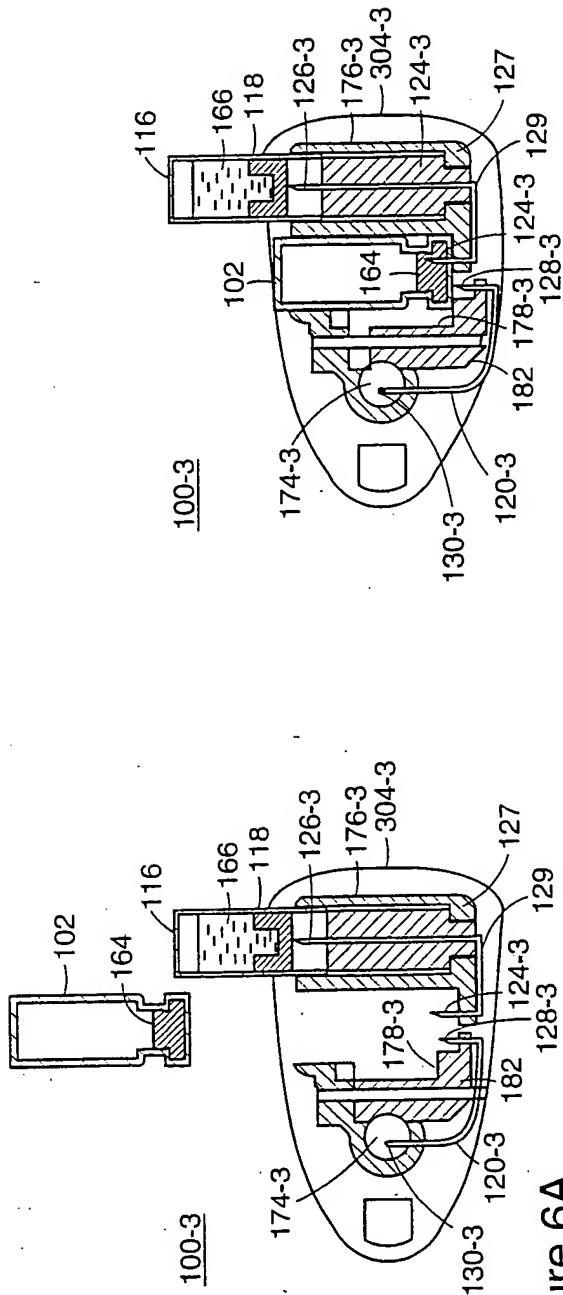


Figure 6B

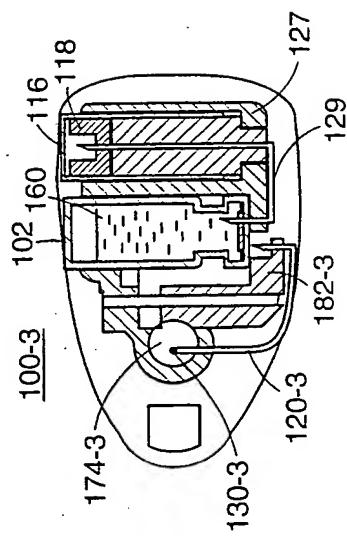


Figure 6C

23/76

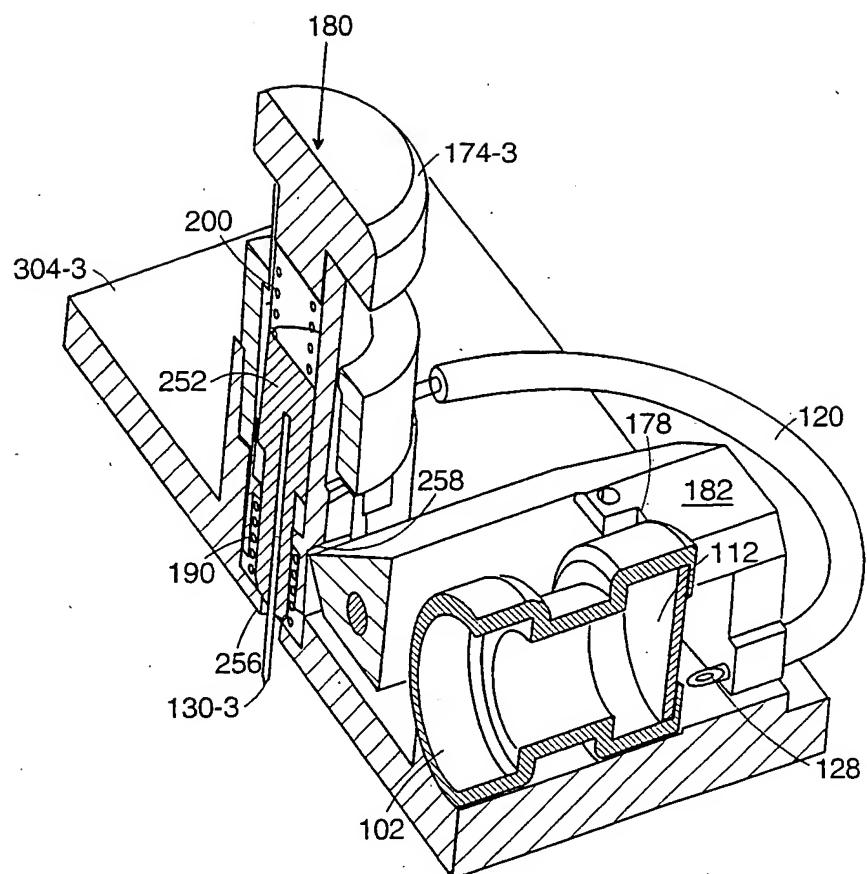
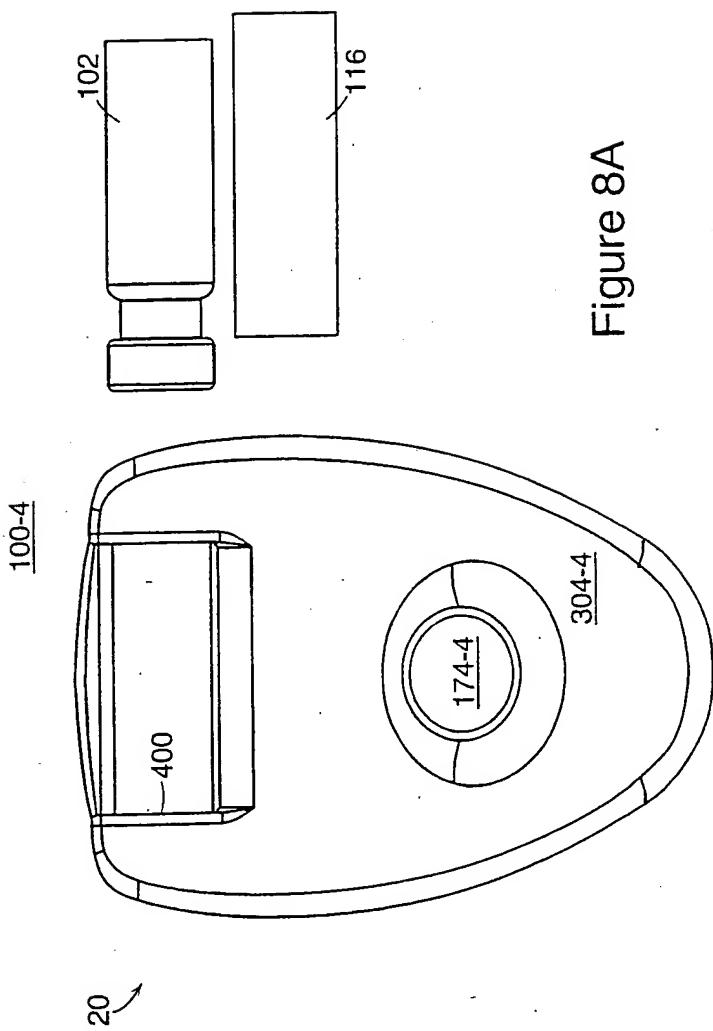


Figure 7B

25/76



27/76

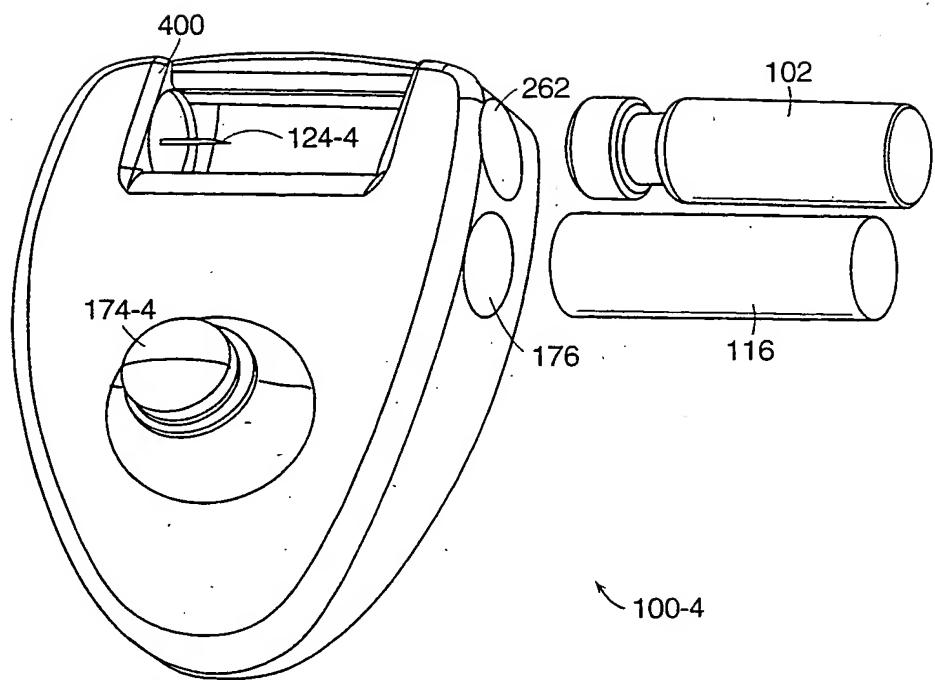


Figure 8D

29/76

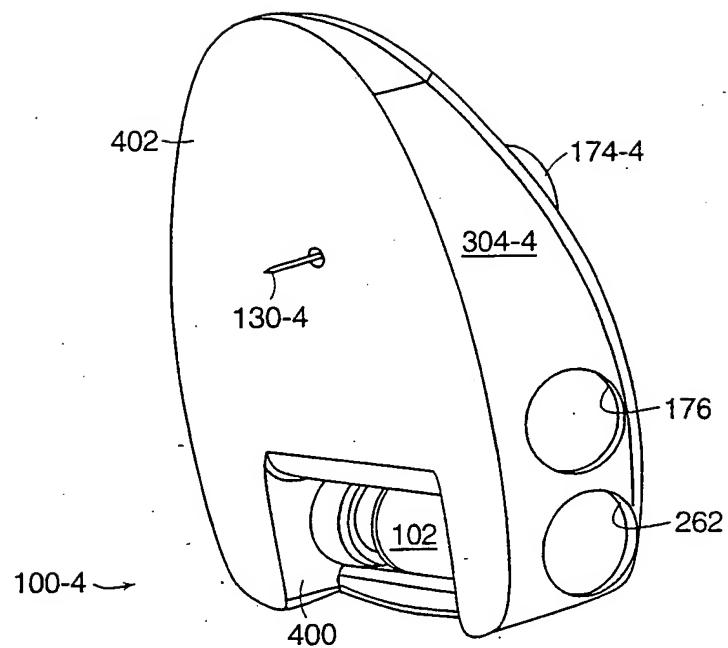


Figure 8F

31/76

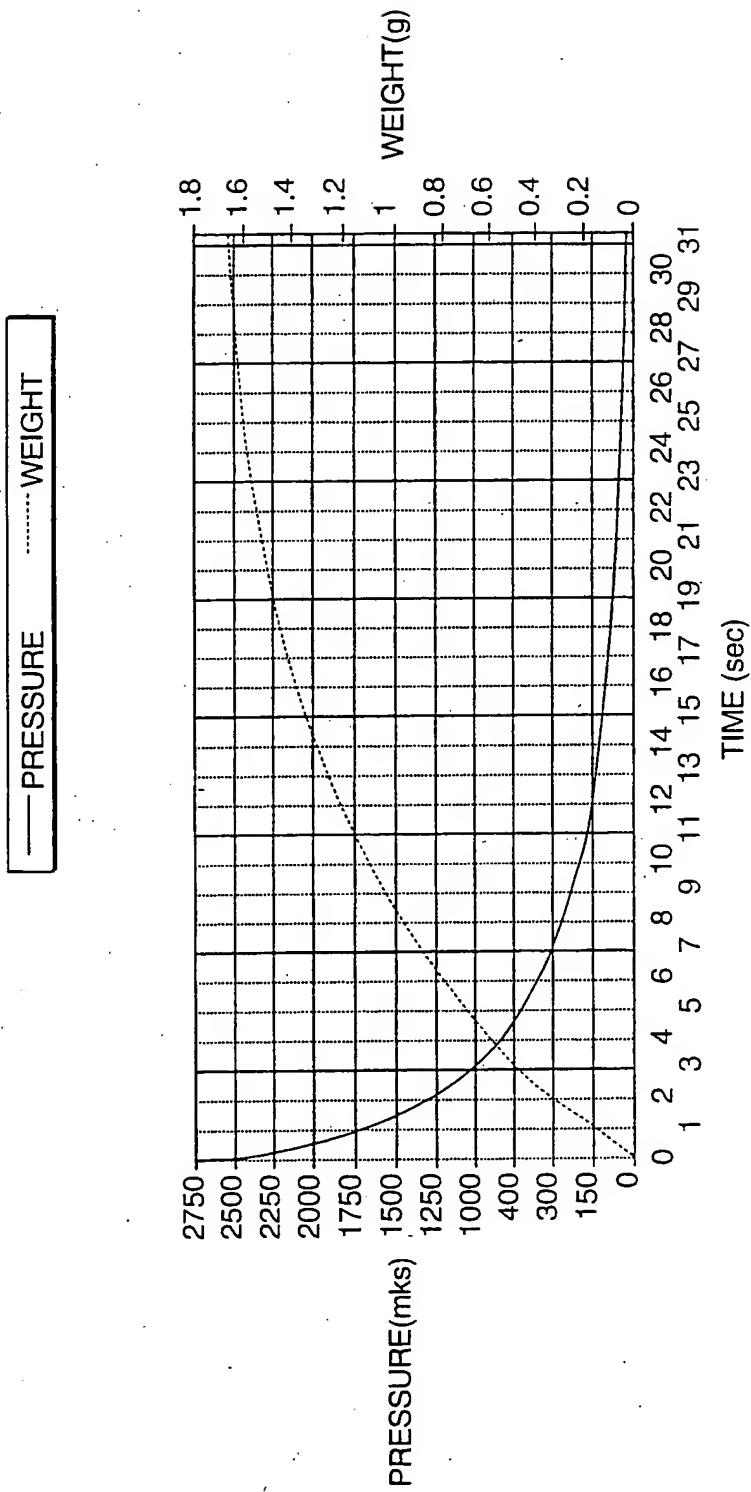


Figure 10A

33/76

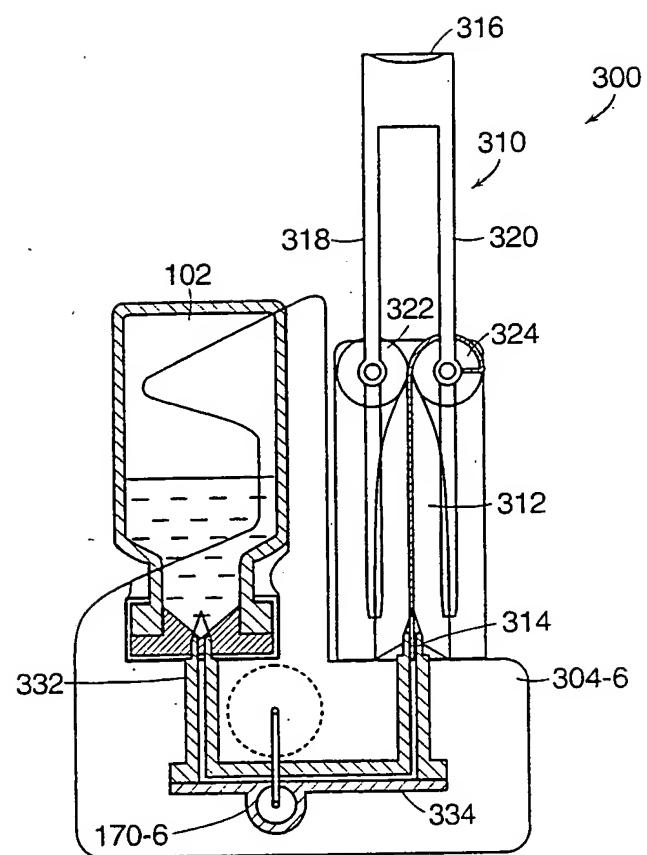


Figure 11A

35/76

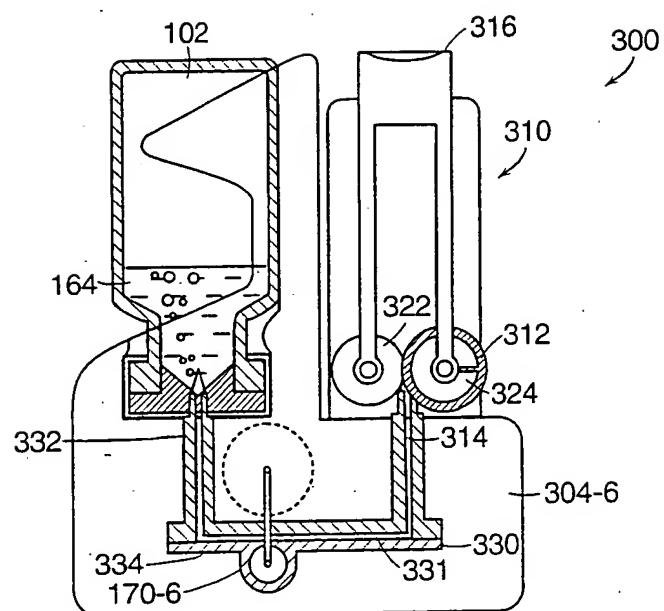


Figure 11D

37/76

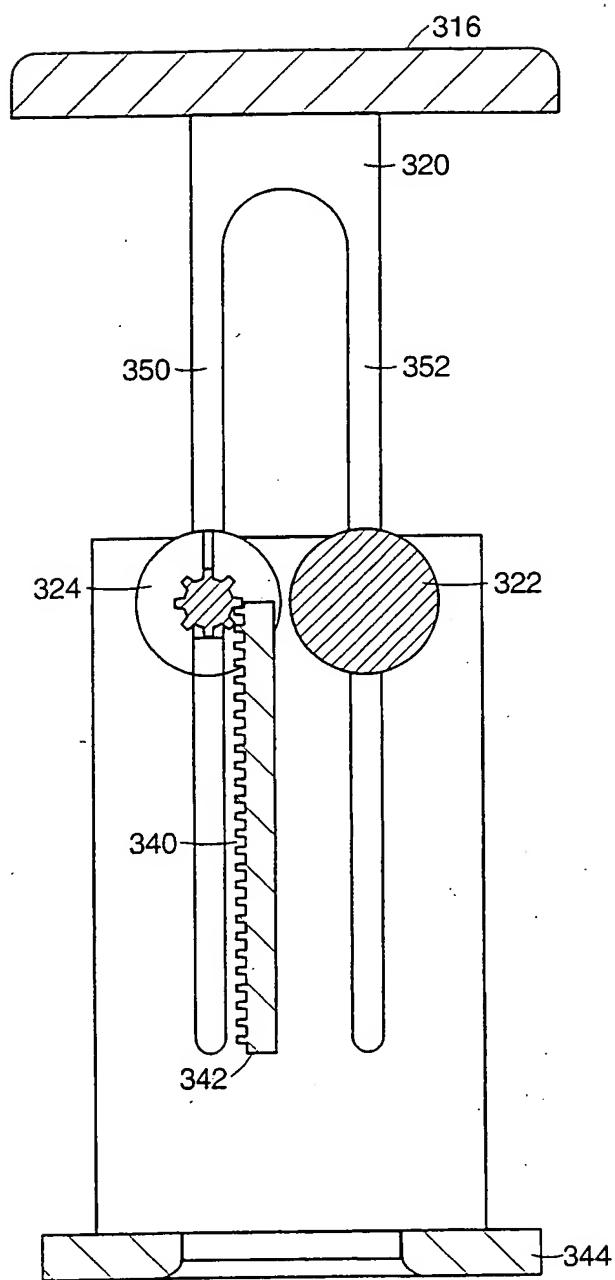


Figure 12B

39/76

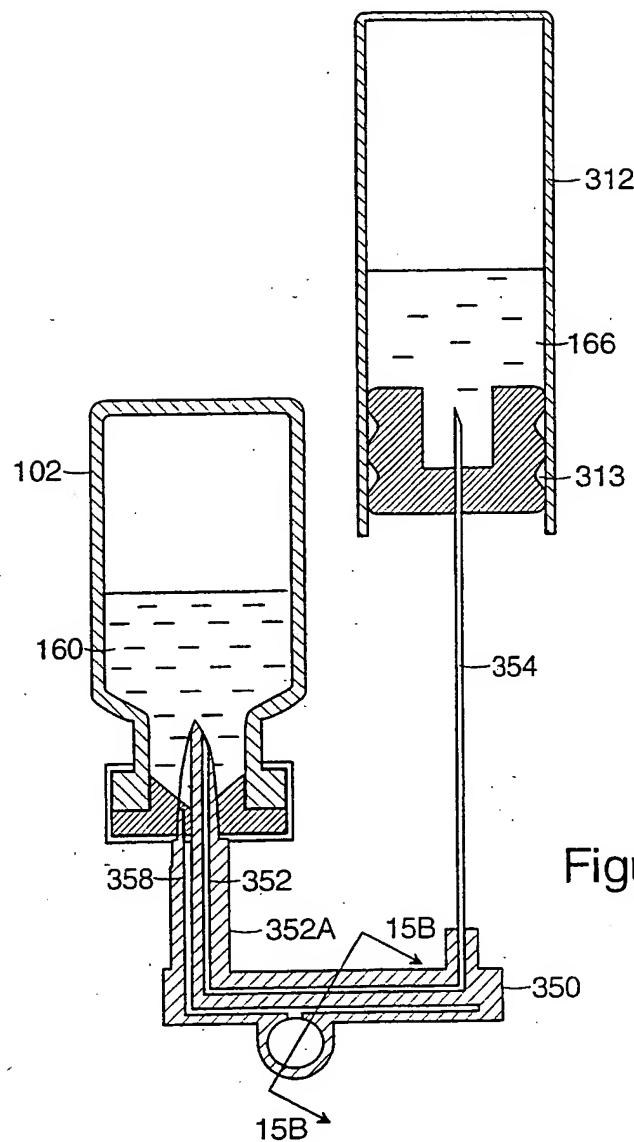


Figure 15A

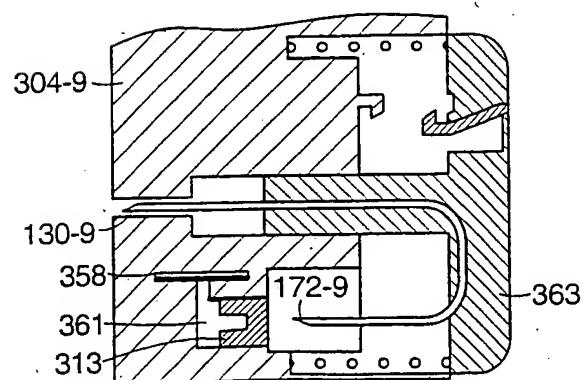


Figure 15B

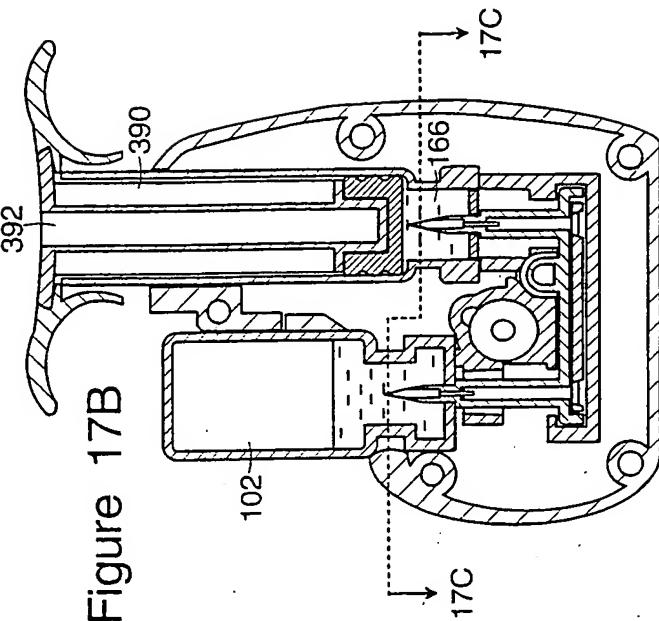


Figure 17B

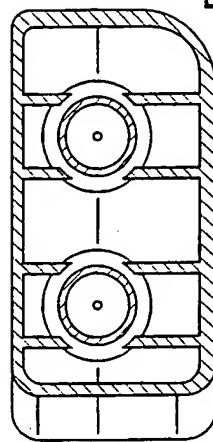


Figure 17C

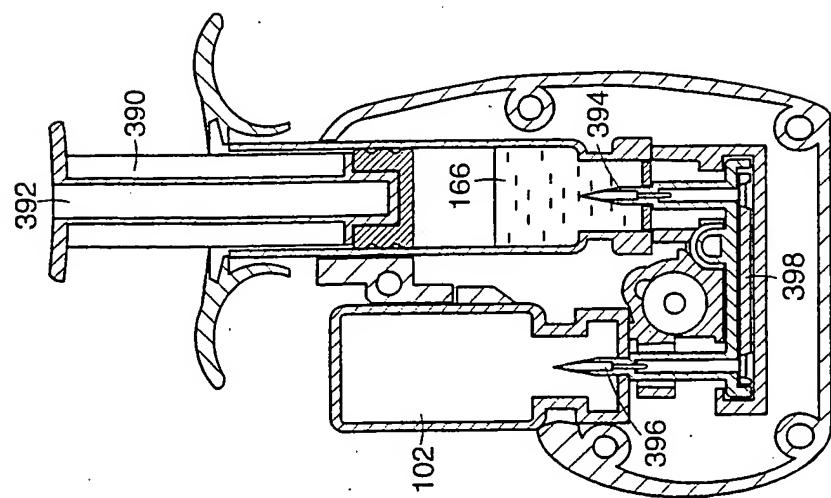


Figure 17A

43/76

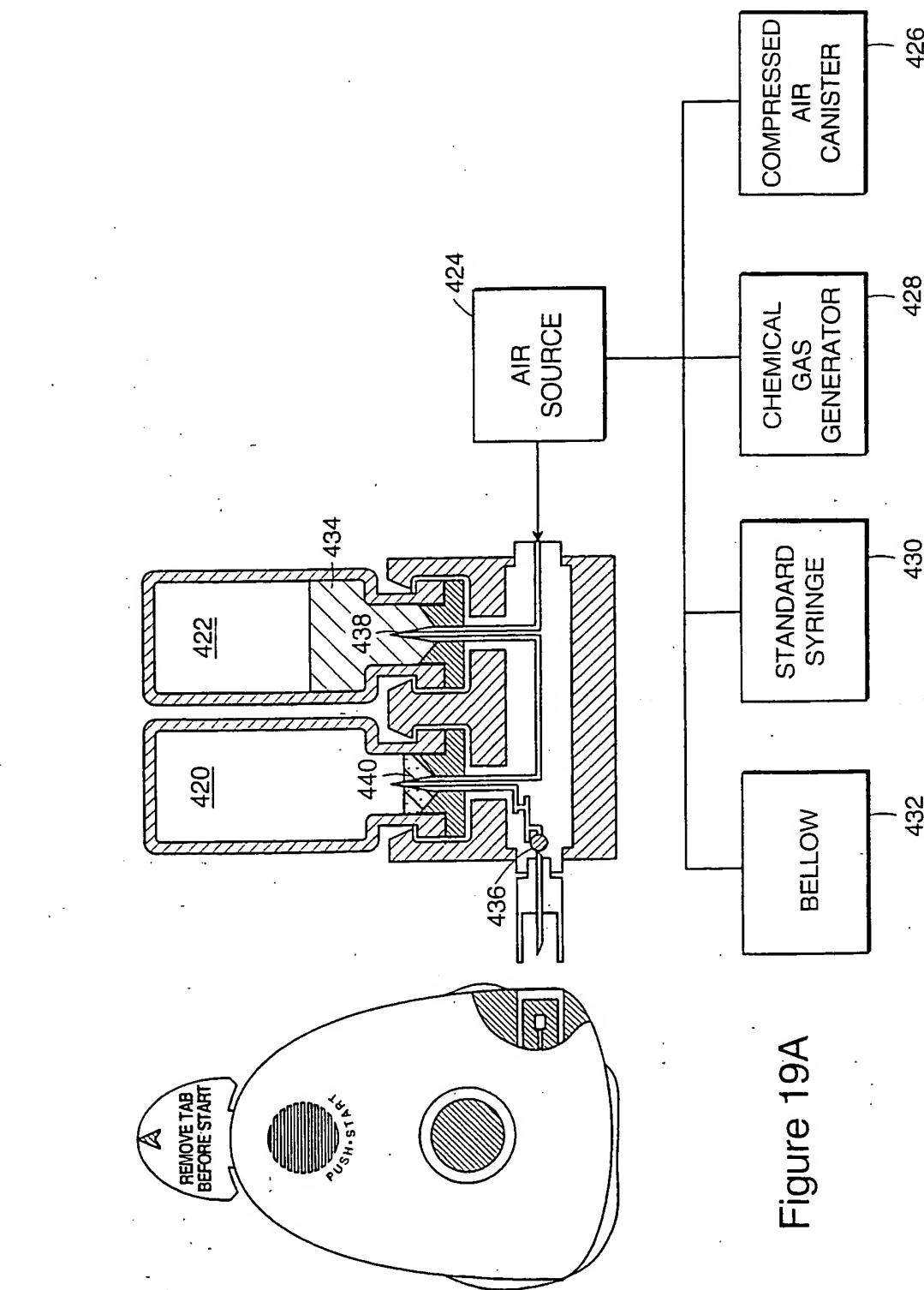


Figure 19A

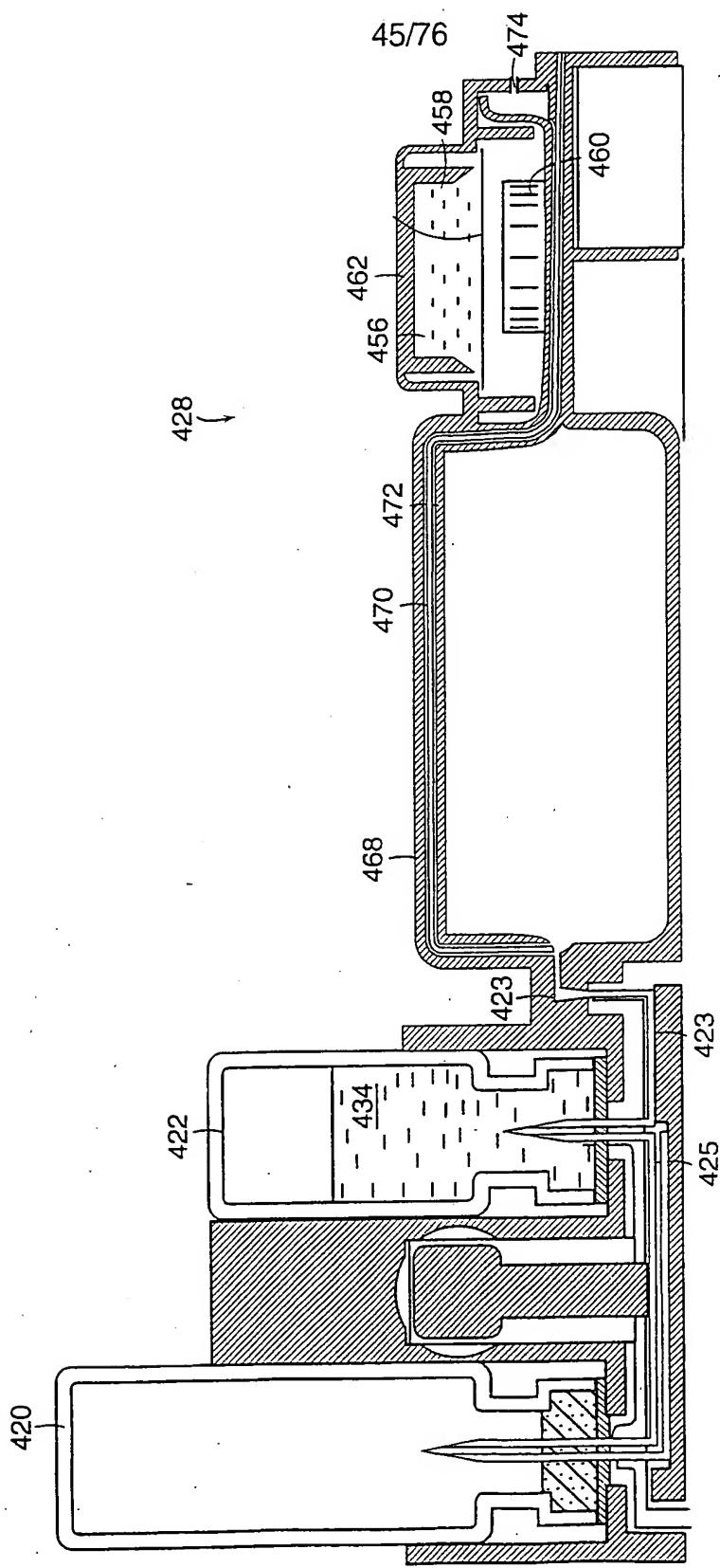


Figure 19C

47/76

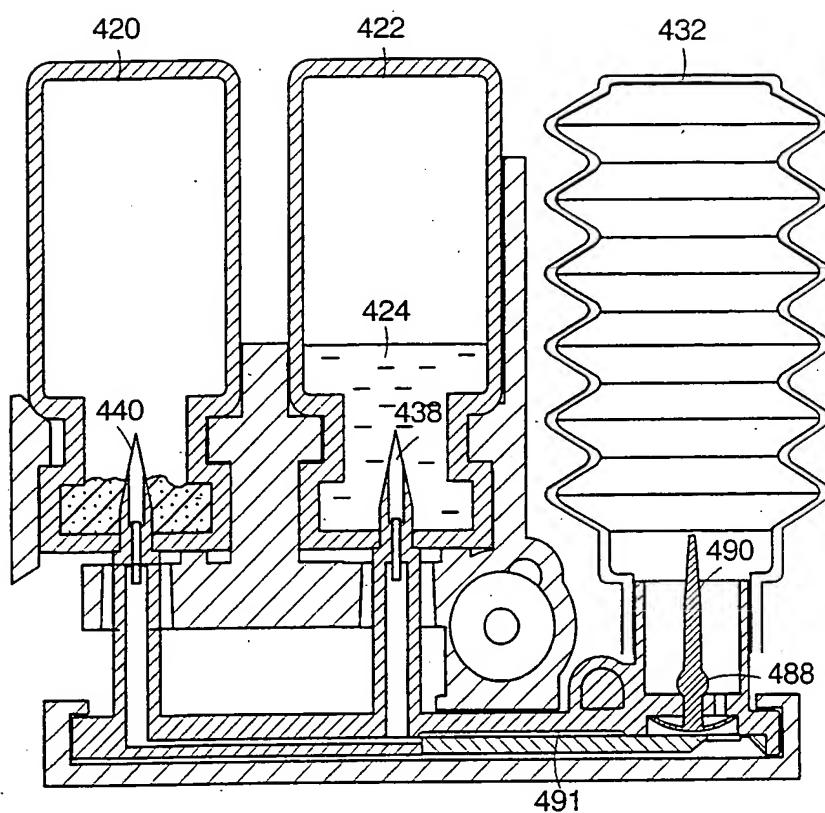


Figure 19E

49/76

Figure 20A-3

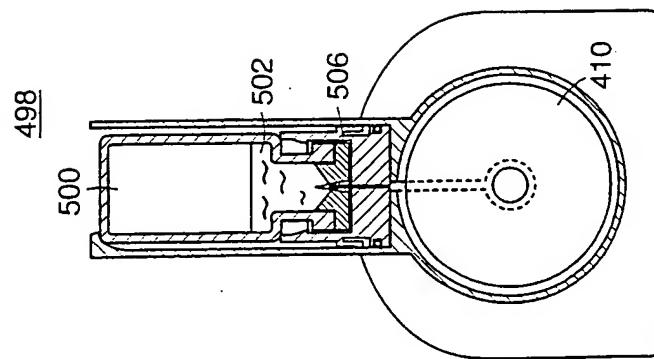


Figure 20A-2

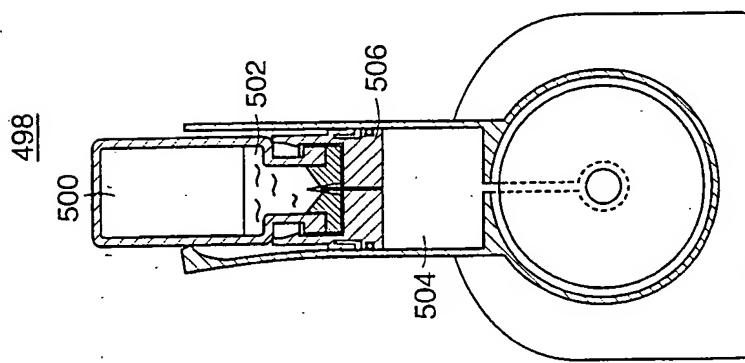
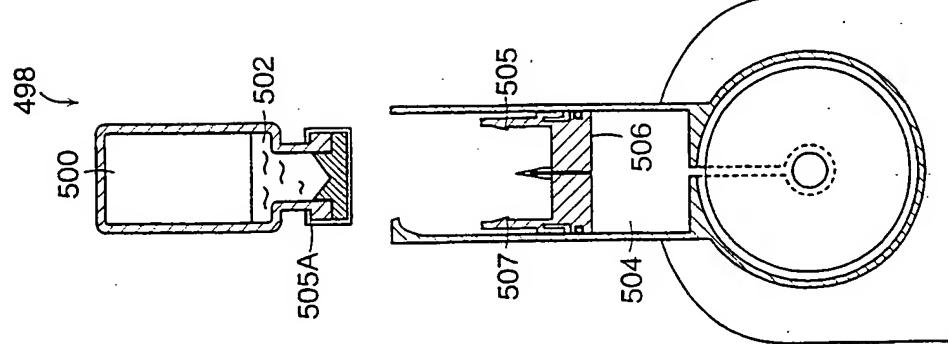


Figure 20A-1



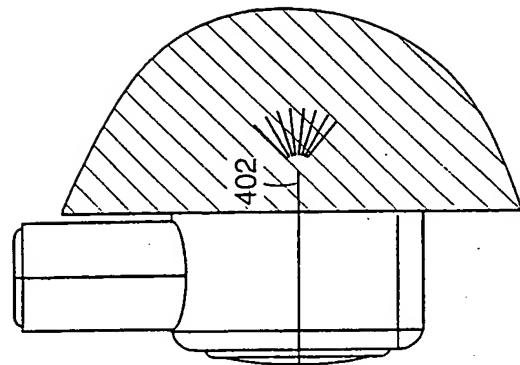


Figure 20C-3

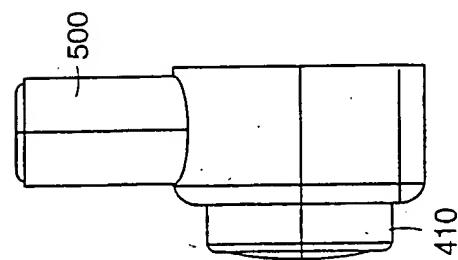


Figure 20C-2

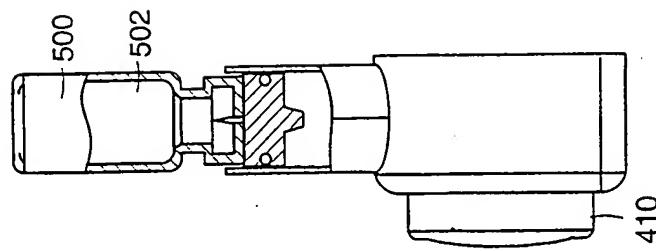


Figure 20C-1

53/76

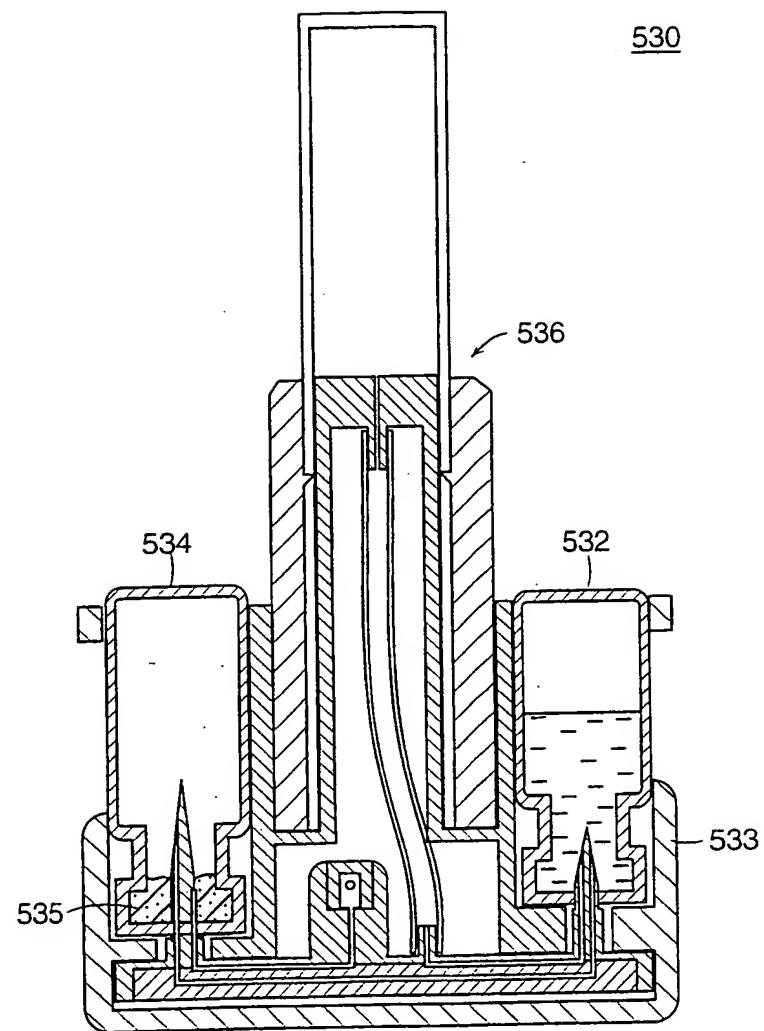


Figure 22A

55/76

540

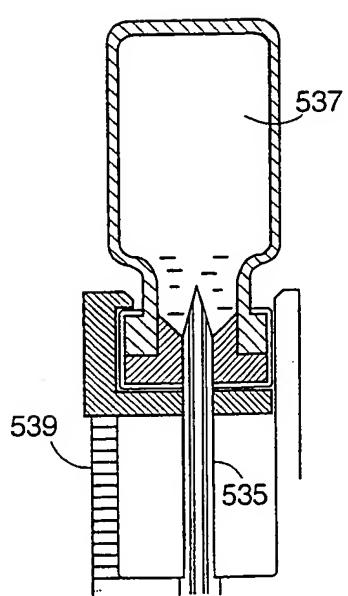


Figure 23A

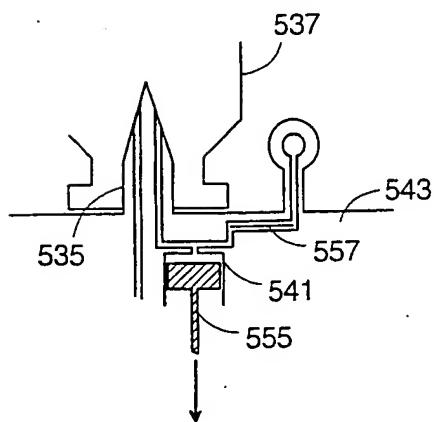


Figure 23B

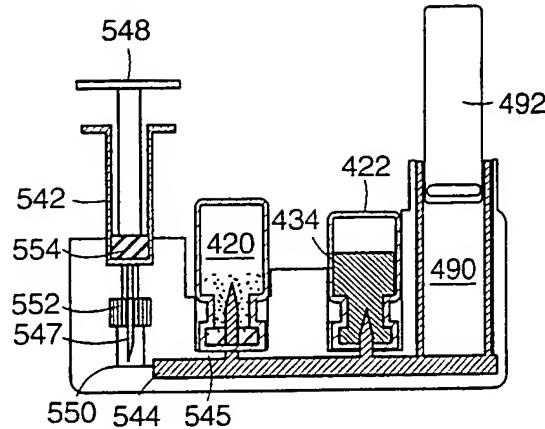


Figure 24A

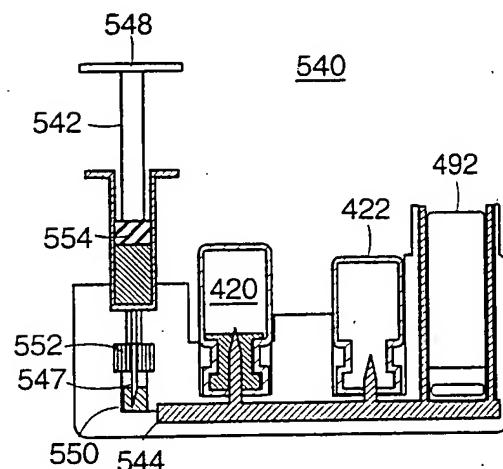


Figure 24B

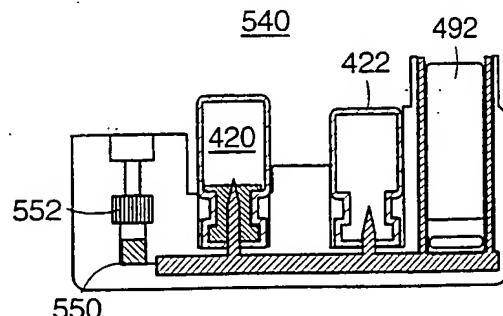


Figure 24C

57/76

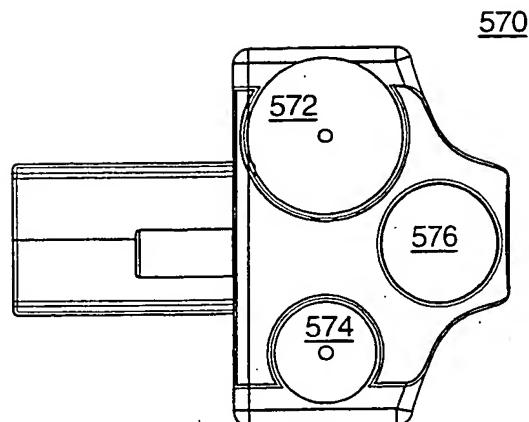


Figure 26A

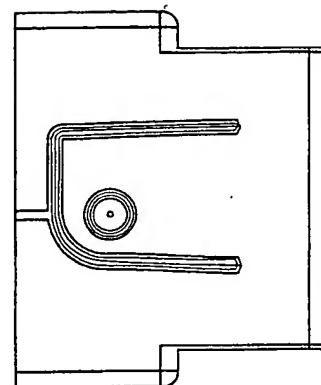


Figure 26B

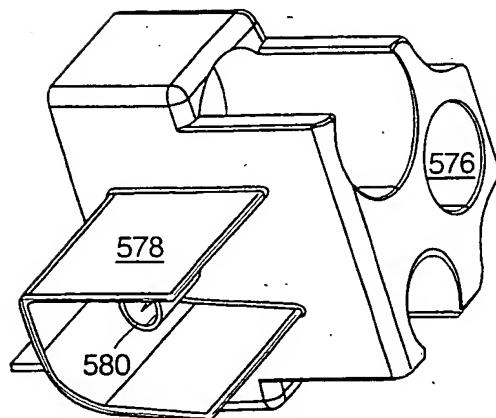


Figure 26C

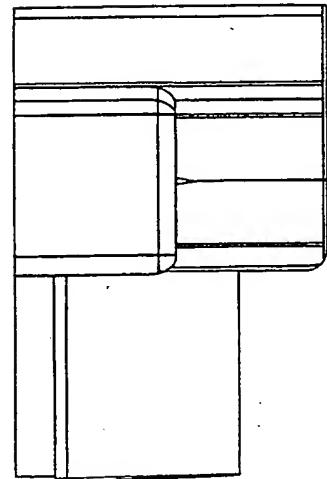


Figure 26D

59/76

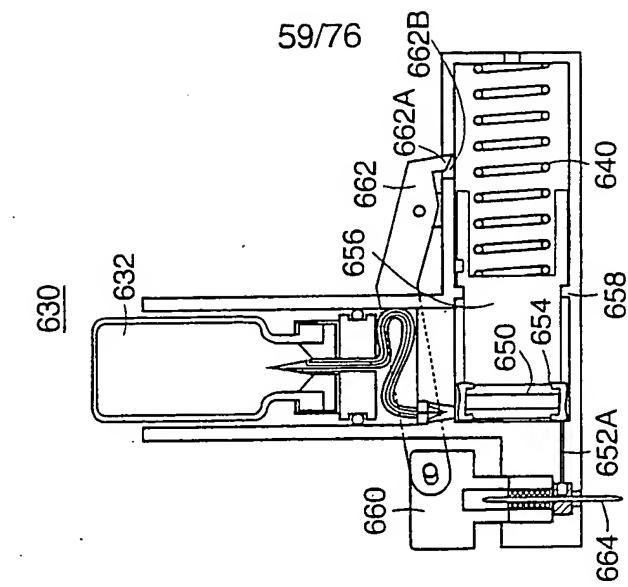


Figure 28C

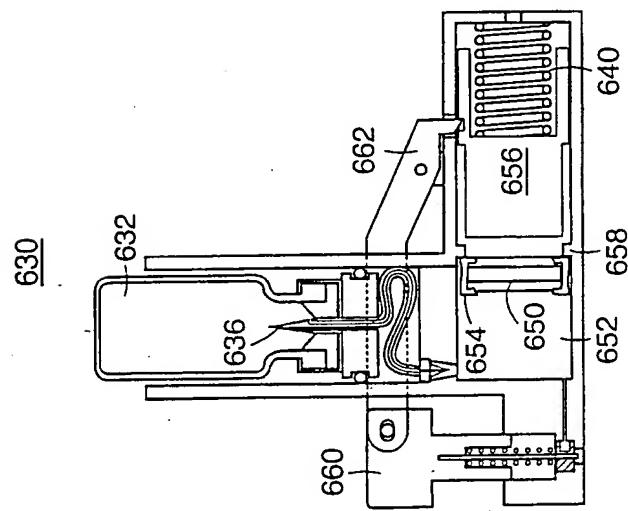


Figure 28B

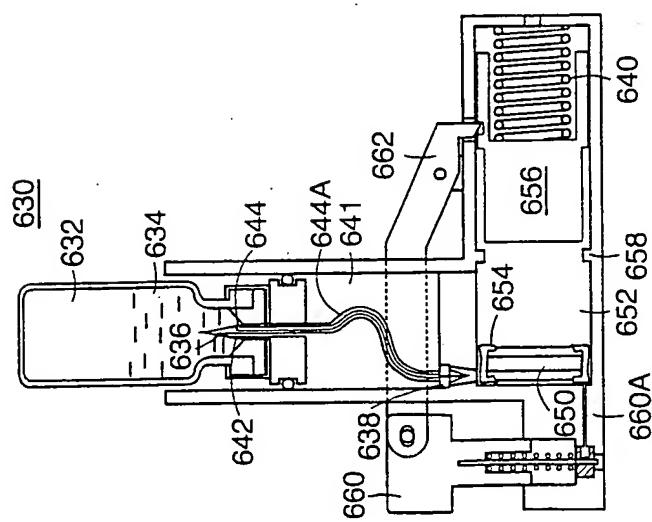


Figure 28A

61/76

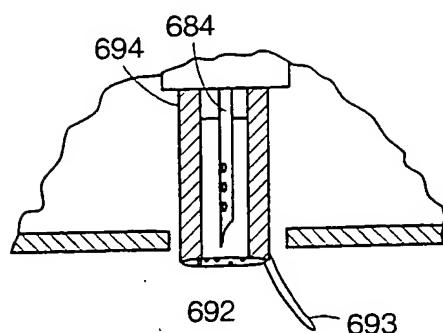


Figure 29A-1

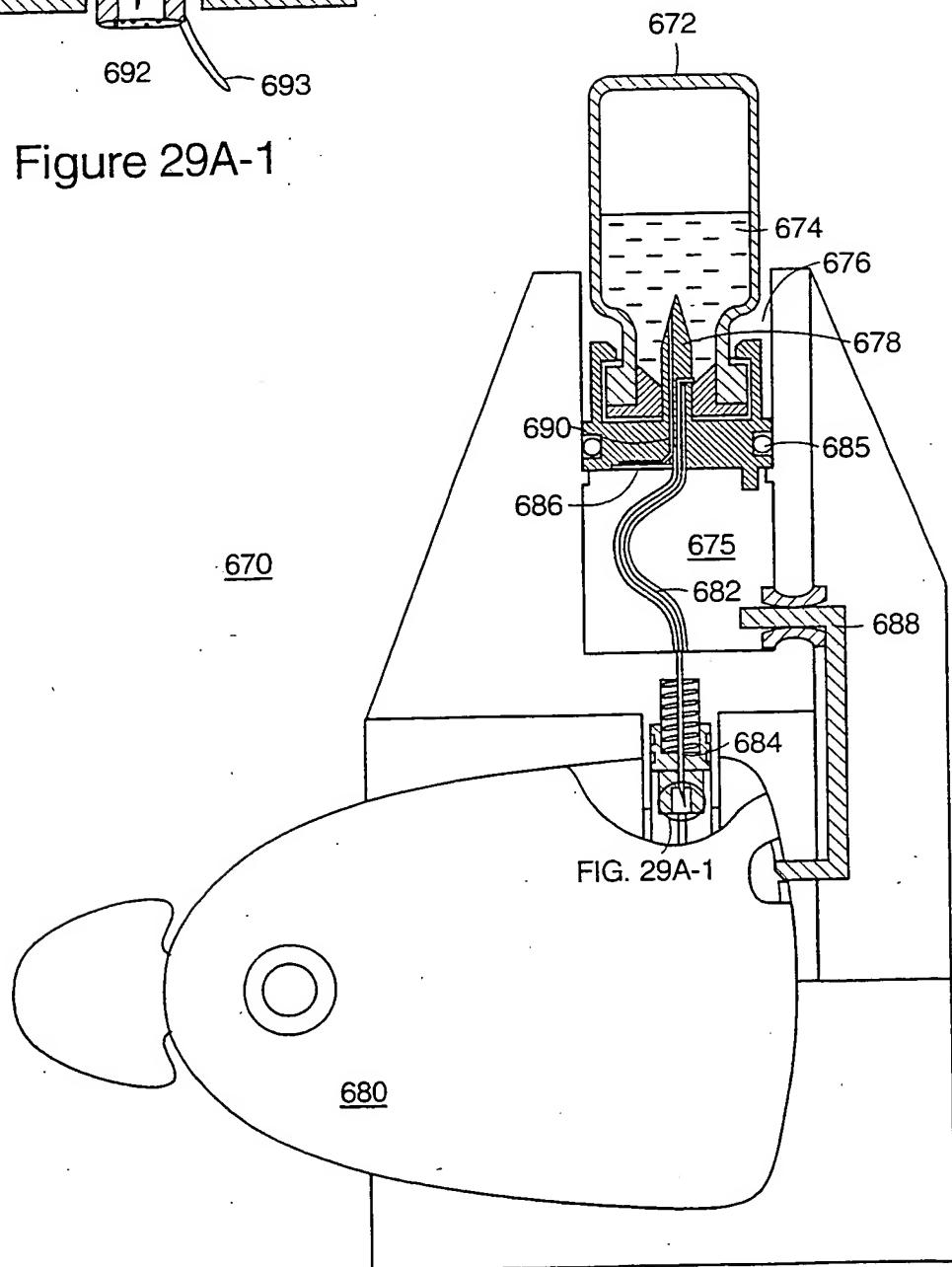


Figure 29A

63/76

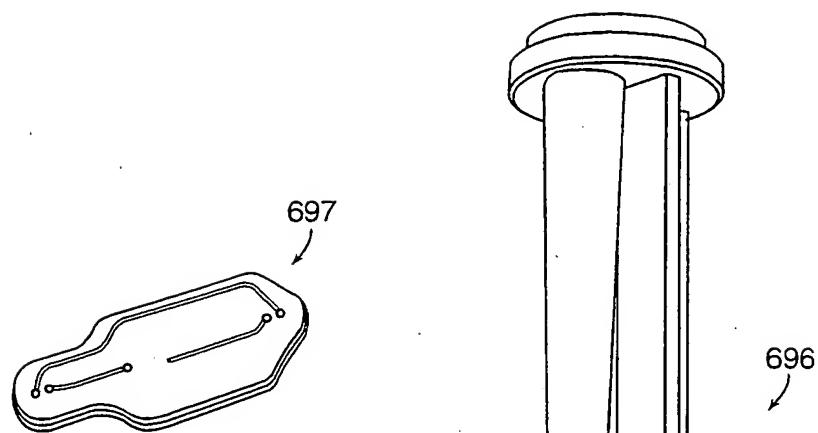


Figure 30B

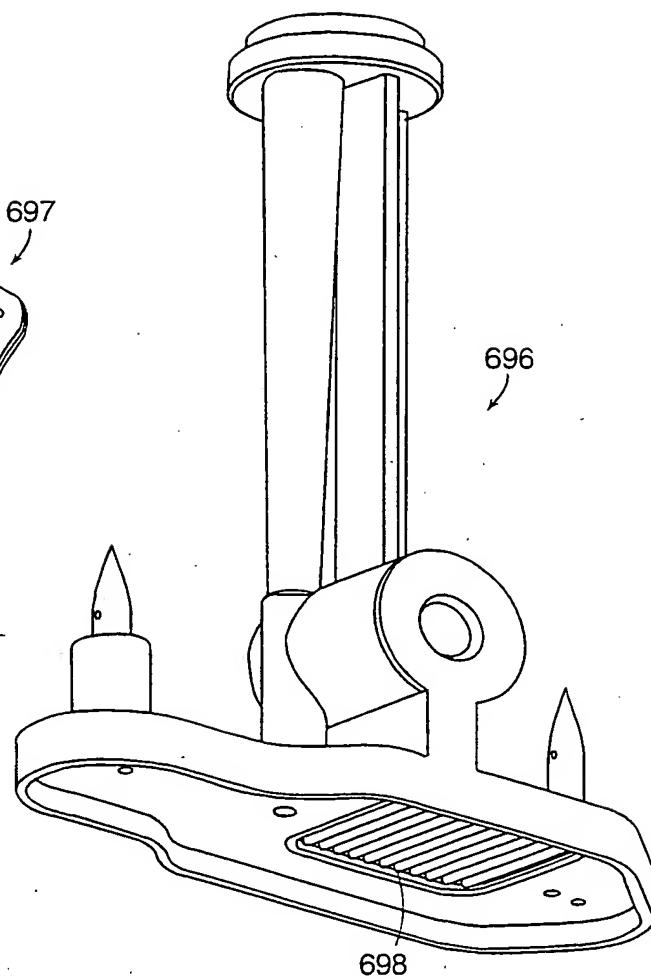


Figure 30A

65/76

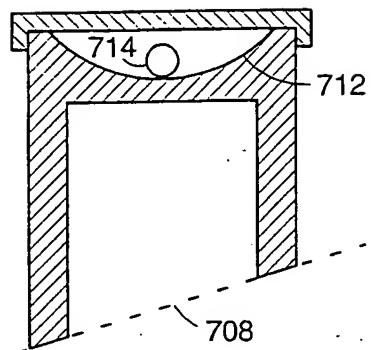
711

Figure 31F

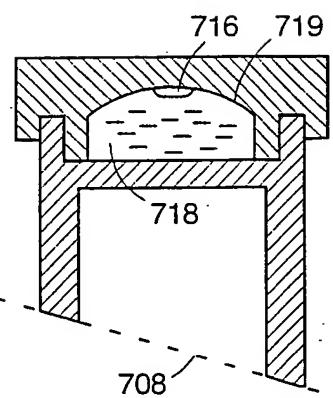
713

Figure 31G

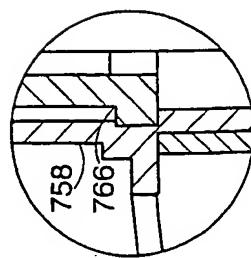
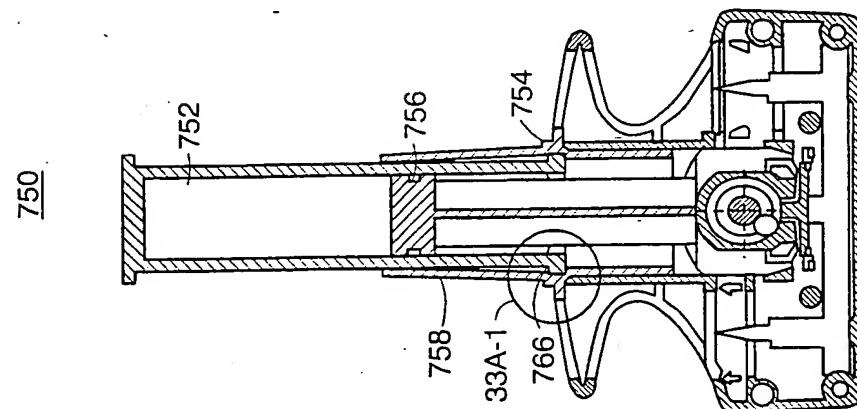
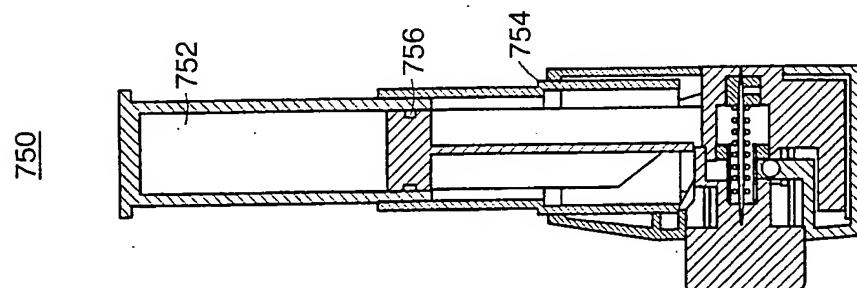
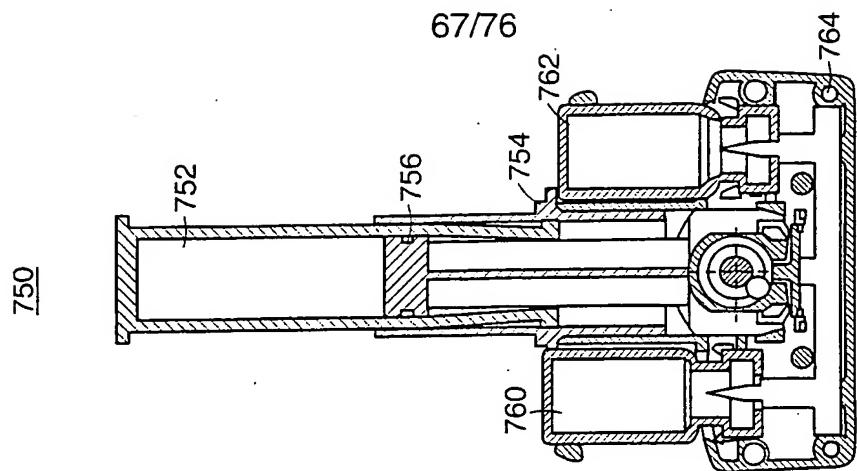


Figure 33A-1

Figure 33C

Figure 33B

Figure 33A

69/76

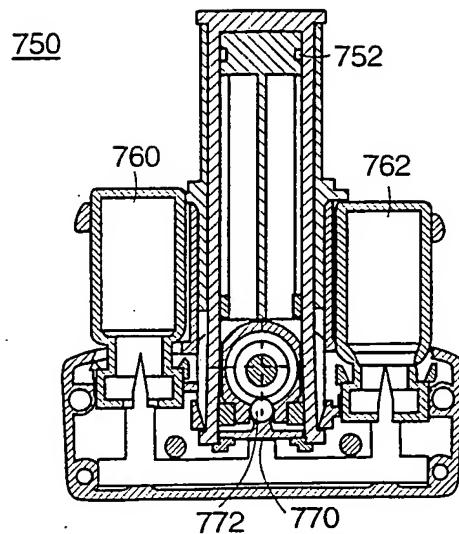


Figure 33H

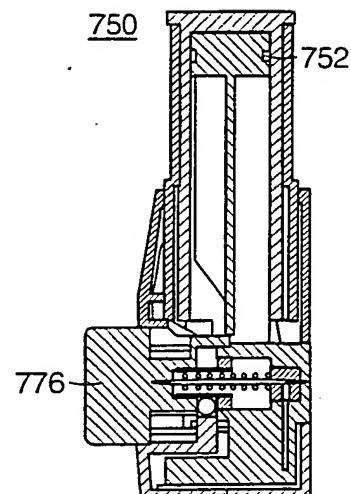


Figure 33I

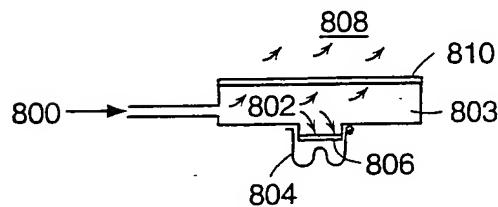


Figure 34A

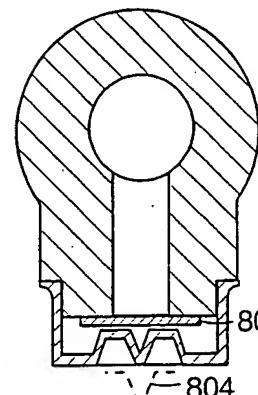


Figure 34C

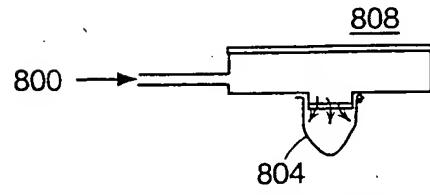


Figure 34B

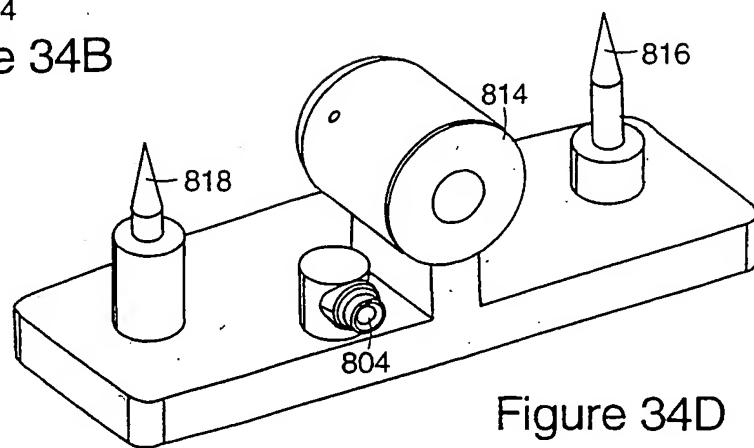


Figure 34D

71/76

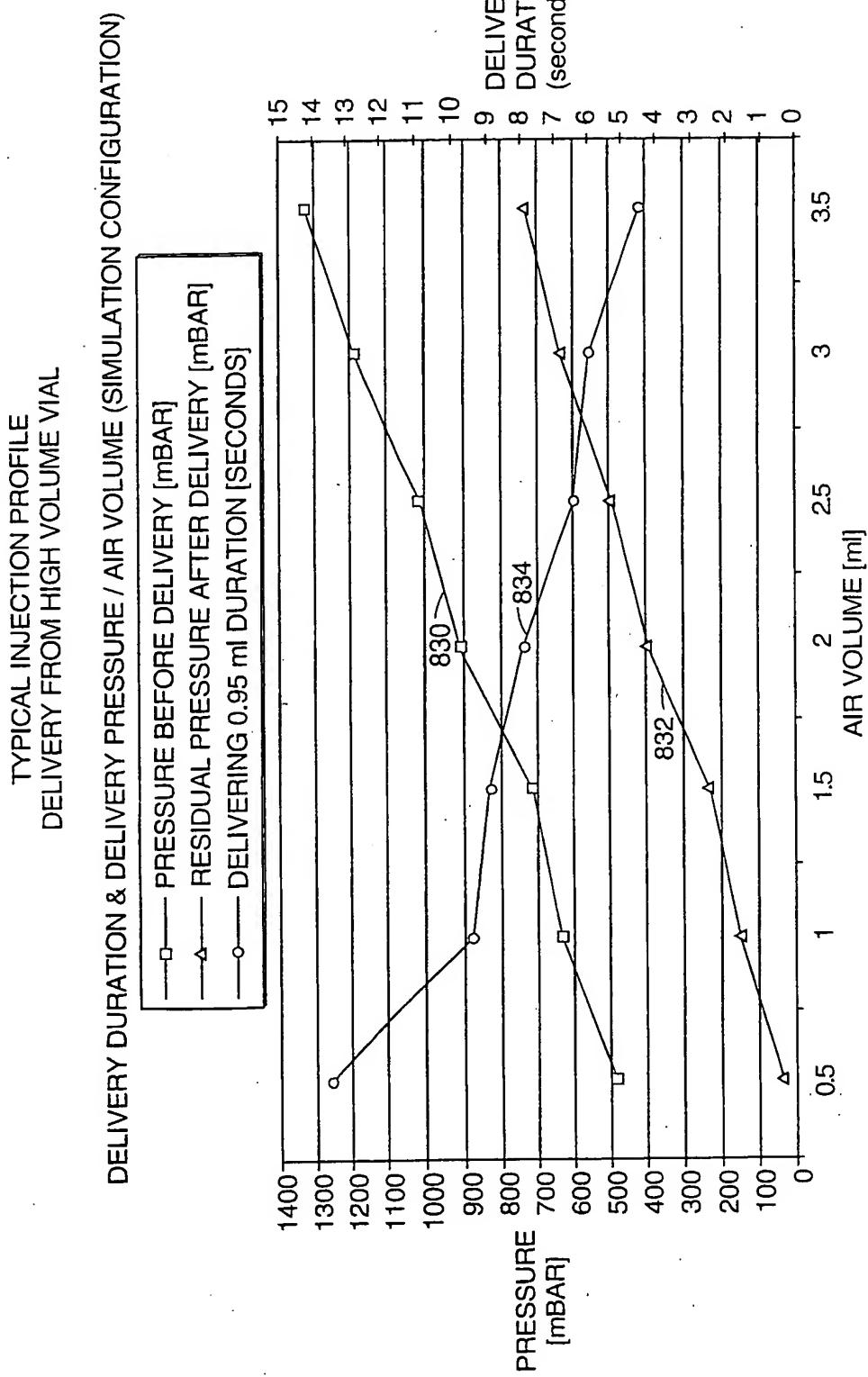


Figure 36

73/76

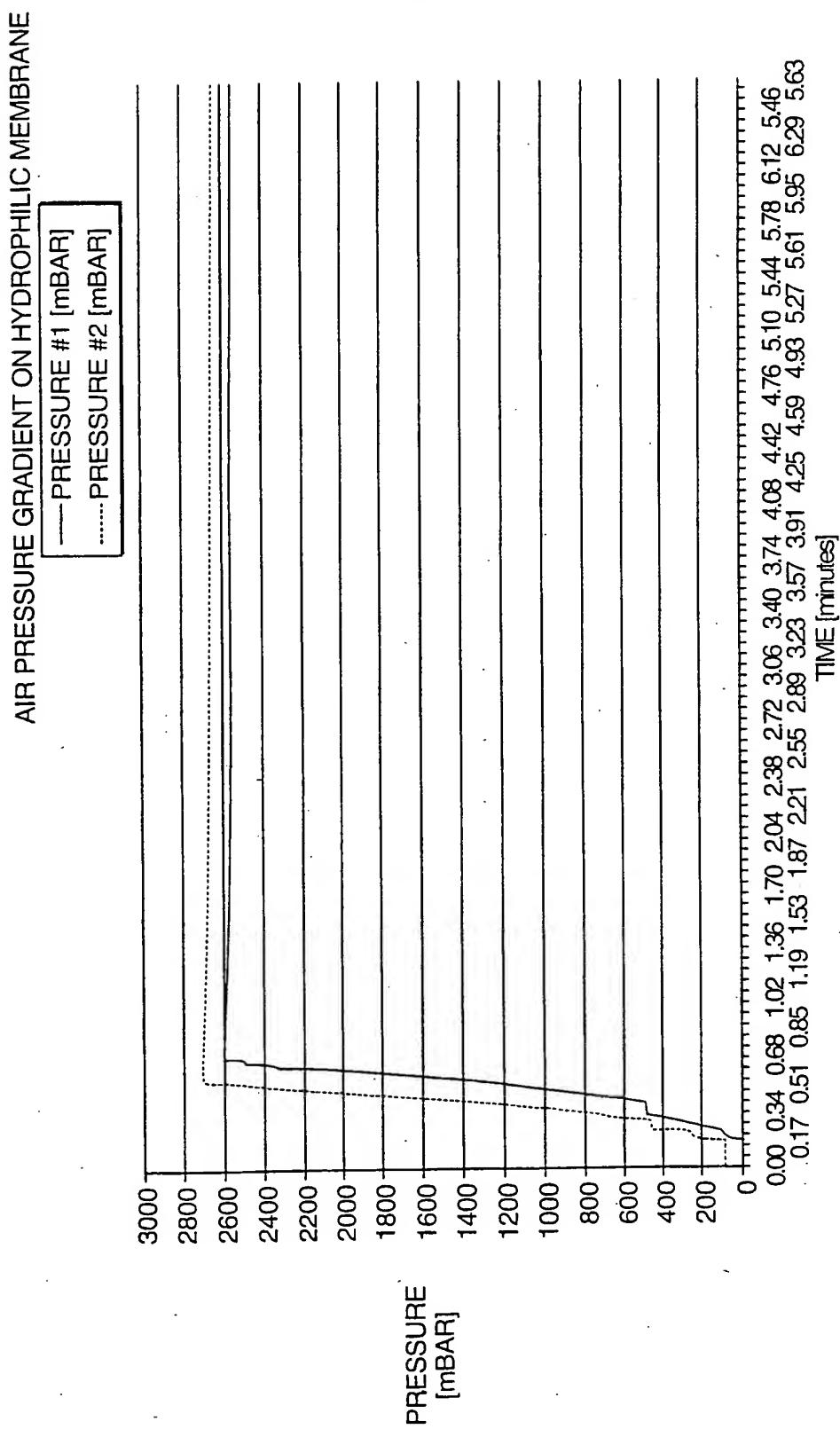


Figure 38

75/76

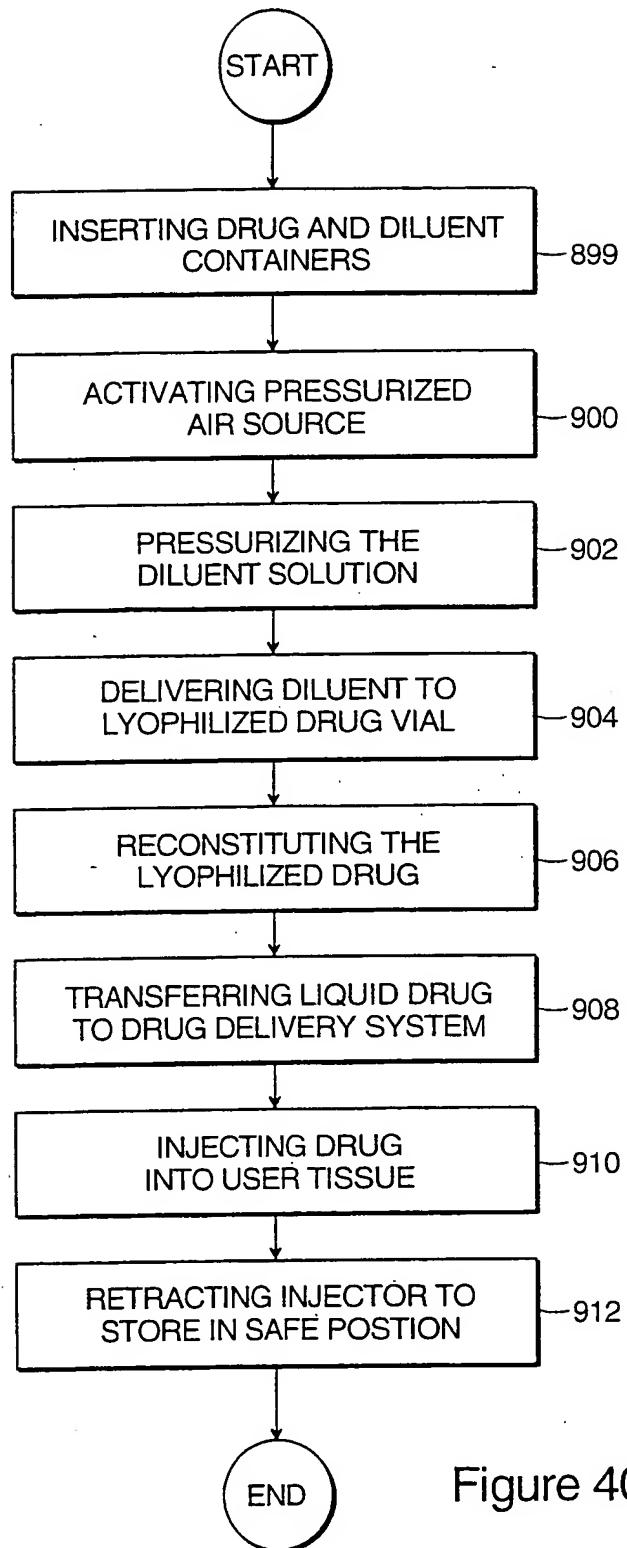


Figure 40

INTERNATIONAL SEARCH REPORT

Inte	rnal Application No
PCT/US 99/26751	

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61M5/24 A61M5/19 A61M5/178

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 755 169 A (SARNOFF STANLEY J ET AL) 5 July 1988 (1988-07-05) column 7, line 12 -column 9, line 20; figures	1,2, 4-12, 18-30
X	US 4 915 689 A (THEEUWES FELIX) 10 April 1990 (1990-04-10) see figures 2 and 8 and their related description	1,2,4,5, 7,8, 11-14, 19,20
X	US 5 329 976 A (HABER TERRY M ET AL) 19 July 1994 (1994-07-19) column 8, line 32 -column 10, line 48; figures	1,2, 4-13, 18-30
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

20 March 2000

28/03/2000

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Clarkson, P

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 26751

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 35-134 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 35-134

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search report has been drawn up for those parts of the application which do appear to be clear (and concise), namely claims 1 to 34.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Serial Application No.

PCT/US 99/26751

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5531683	A	AU 6770694 A WO 9528201 A		10-11-1995 26-10-1995
US 4915688	A	10-04-1990	NONE	
WO 9710012	A	20-03-1997	IE 77523 B AU 7093496 A CA 2231542 A EP 0850076 A NO 980963 A NZ 318852 A US 5814020 A	17-12-1997 01-04-1997 20-03-1997 01-07-1998 07-05-1998 28-10-1998 29-09-1998
US 4850978	A	25-07-1989	AU 604594 B AU 2801489 A CA 1297751 A DE 3869124 A EP 0340297 A ES 2009094 A IL 88226 A JP 6014977 B JP 2501986 T KR 9605820 B MX 165876 B TR 23542 A WO 8903703 A ZA 8808105 A	20-12-1990 23-05-1989 24-03-1992 16-04-1992 08-11-1989 16-08-1989 15-11-1992 02-03-1994 05-07-1990 01-05-1996 08-12-1992 22-03-1990 05-05-1989 26-07-1989
US 5707365	A	13-01-1998	NONE	
US 5147323	A	15-09-1992	AU 653227 B AU 1678192 A AU 2263692 A CA 2101929 A CA 2101930 A CN 1064621 A, B CN 1065020 A, B EP 0574544 A EP 0574553 A JP 6505415 T JP 6510442 T WO 9215346 A WO 9215347 A US 5199949 A US 5240146 A US 5262222 A	22-09-1994 06-10-1992 06-10-1992 09-09-1992 09-09-1992 23-09-1992 07-10-1992 22-12-1993 22-12-1993 23-06-1994 24-11-1994 17-09-1992 17-09-1992 06-04-1993 31-08-1993 20-02-1994



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61M 5/24, 5/19, 5/178		A1	(11) International Publication Number: WO 00/29049
			(43) International Publication Date: 25 May 2000 (25.05.00)
<p>(21) International Application Number: PCT/US99/26751</p> <p>(22) International Filing Date: 12 November 1999 (12.11.99)</p> <p>(30) Priority Data: 60/108,382 13 November 1998 (13.11.98) US 60/131,644 29 April 1999 (29.04.99) US</p> <p>(71) Applicant (for all designated States except US): ELAN PHARMA INTERNATIONAL LIMITED [IE/IE]; Lincoln House, Lincoln Place, Dublin 2 (IE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): LAVI, Gilad [IL/IL]; Harav Bazov David 6, 58497 Holon (IL). YIGAL, Gil [IL/IL]; Shlom Zion 5/7, Gan-Yavne 60800 (IL). TSALS, Izrail [US/US]; 17 Rose Way, Sudbury, MA 01776 (US). GROSS, Yossi [IL/IL]; Moshav Mazor 20502 (IL).</p> <p>(74) Agents: HOOVER, Thomas, O. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>	
<p>(54) Title: DRUG DELIVERY SYSTEMS AND METHODS</p> <p>(57) Abstract</p> <p>The present invention relates to a drug delivery device for mixing and delivering a drug by injection. The device includes a housing having a first port or opening therein that receives a first container that contains a fluid or powdered drug, for example, a lyophilized drug. The housing can also include a second port or opening that receives a second container that contains a fluid to be mixed with the drug to form an injectable fluid. The device includes a manifold having a channel that fluidly connects the first and second containers. A penetrating membrane such as a needle is used to inject the drug into a patient which is in fluid communication with the first container. The needle is movable from a storage position in the housing to an injection position extending through the housing.</p> <img alt="Technical drawing of a drug delivery system showing a housing with various components labeled with numbers. The drawing illustrates a housing (102) with a port (100) at the top, a manifold (304) with a channel (122), and a needle assembly (110) that can be moved between a storage position (106) and an injection position (118). Various other parts are labeled with numbers such as 132, 133, 134, 140, 142, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596, 598, 600, 602, 604, 606, 608, 610, 612, 614, 616, 618, 620, 622, 624, 626, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 666, 668, 670, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 702, 704, 706, 708, 710, 712, 714, 716, 718, 720, 722, 724, 726, 728, 730, 732, 734, 736, 738, 740, 742, 744, 746, 748, 750, 752, 754, 756, 758, 760, 762, 764, 766, 768, 770, 772, 774, 776, 778, 780, 782, 784, 786, 788, 790, 792, 794, 796, 798, 800, 802, 804, 806, 808, 810, 812, 814, 816, 818, 820, 822, 824, 826, 828, 830, 832, 834, 836, 838, 840, 842, 844, 846, 848, 850, 852, 854, 856, 858, 860, 862, 864, 866, 868, 870, 872, 874, 876, 878, 880, 882, 884, 886, 888, 890, 892, 894, 896, 898, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, 944, 946, 948, 950, 952, 954, 956, 958, 960, 962, 964, 966, 968, 970, 972, 974, 976, 978, 980, 982, 984, 986, 988, 990, 992, 994, 996, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, 1085, 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 12210, 12211, 12212, 12213, 12214, 12215, 12216, 12217, 12218, 12219, 12220, 12221, 12222, 12223, 12224, 12225, 12226, 12227, 12228, 12229, 122210, 122211, 122212, 122213, 122214, 122215, 122216, 122217, 122218, 122219, 122220, 122221, 122222, 122223, 122224, 122225, 122226, 122227, 122228, 122229, 1222210, 1222211, 1222212, 1222213, 1222214, 1222215, 1222216, 1222217, 1222218, 1222219, 1222220, 1222221, 1222222, 1222223, 1222224, 1222225, 1222226, 1222227, 1222228, 1222229, 12222210, 12222211, 12222212, 12222213, 12222214, 12222215, 12222216, 12222217, 12222218, 12222219, 12222220, 12222221, 12222222, 12222223, 12222224, 12222225, 12222226, 12222227, 12222228, 12222229, 122222210, 122222211, 122222212, 122222213, 122222214, 122222215, 122222216, 122222217, 122222218, 122222219, 122222220, 122222221, 122222222, 122222223, 122222224, 122222225, 122222226, 122222227, 122222228, 122222229, 1222222210, 1222222211, 1222222212, 1222222213, 1222222214, 1222222215, 1222222216, 1222222217, 1222222218, 1222222219, 1222222220, 1222222221, 1222222222, 1222222223, 1222222224, 1222222225, 1222222226, 1222222227, 1222222228, 1222222229, 12222222210, 12222222211, 12222222212, 12222222213, 12222222214, 12222222215, 12222222216, 12222222217, 12222222218, 12222222219, 12222222220, 12222222221, 12222222222, 12222222223, 12222222224, 12222222225, 12222222226, 12222222227, 12222222228, 12222222229, 122222222210, 122222222211, 122222222212, 122222222213, 122222222214, 122222222215, 122222222216, 122222222217, 122222222218, 122222222219, 122222222220, 122222222221, 122222222222, 122222222223, 122222222224, 122222222225, 122222222226, 122222222227, 122222222228, 122222222229, 1222222222210, 1222222222211, 1222222222212, 1222222222213, 1222222222214, 1222222222215, 1222222222216, 1222222222217, 1222222222218, 1222222222219, 1222222222220, 1222222222221, 1222222222222, 1222222222223, 1222222222224, 1222222222225, 1222222222226, 1222222222227, 1222222222228, 1222222222229, 12222222222210, 12222222222211, 12222222222212, 12222222222213, 12222222222214, 12222222222215, 12222222222216, 12222222222217, 12222222222218, 12222222222219, 12222222222220, 12222222222221, 12222222222222, 12222222222223, 12222222222224, 12222222222225, 12222222222226, 12222222222227, 12222222222228, 12222222222229, 122222222222210, 122222222222211, 122222222222212, 122222222222213, 122222222222214, 122222222222215, 122222222222216, 122222222222217, 122222222222218, 122222222222219, 122222222222220, 122222222222221, 122222222222222, 122222222222223, 122222222222224, 122222222222225, 122222222222226, 122222222222227, 122222222222228, 122222222222229, 1222222222222210, 1222222222222211, 1222222222222212, 1222222222222213, 1222222222222214, 1222222222222215, 1222222222222216, 1222222222222217, 1222222222222218, 1222222222222219, 1222222222222220, 1222222222222221, 1222222222222222, 1222222222222223, 1222222222222224, 1222222222222225, 1222222222222226, 1222222222222227, 1222222222222228, 1222222222222229, 12222222222222210, 12222222222222211, 12222222222222212, 12222222222222213, 12222222222222214, 12222222222222215, 12222222222222216, 12222222222222217, 12222222222222218, 12222222222222219, 12222222222222220, 12222222222222221, 12222222222222222, 12222222222222223, 12222222222222224, 12222222222222225, 12222222222222226, 12222222222222227, 12222222222222228, 12222222222222229, 122222222222222210, 122222222222222211, 122222222222222212, 122222222222222213, 122222222222222214, 122222222222222215, 122222222222222216, 122222222222222217, 122222222222222218, 122222222222222219, 122222222222222220, 122222222222222221, 122222222222222222, 122222222222222223, 122222222222222224, 122222222222222225, 122222222222222226, 122222222222222227, 122222222222222228, 122222222222222229, 1222222222222222210, 1222222222222222211, 1222222222222222212, 1222222222222222213, 1222222222222222214, 1222222222222222215, 1222222222222222216, 1222222222222222217, 1222222222222222218, 1222222222222222219, 1222222222222222220, 1222222222222222221, 1222222222222222222, 1222222222222222223, 1222222222222222224, 1222222222222222225, 1222222222222222226, 1222222222222222227, 1222222222222222228, 1222222222222222229, 12222222222222222210, 12222222222222222211, 12222222222222222212, 12222222222222222213, 12222222222222222214, 12222222222222222215, 12222222222222222216, 12222222222222222217, 12222222222222222218, 12222222222222222219, 12222222222222222220, 12222222222222222221, 12222222222222222222, 12222222222222222223, 12222222222222222224, 12222222222222222225, 12222222222222222226, 12222222222222222227, 12222222222222222228, 12222222222222222229, 122222222222222222210, 122222222222222222211, 122222222222222222212, 122222222222222222213, 122222222222222222214, 122222222222222222215, 122222222222222222216, 122222222222222222217, 122222222222222222218, 122222222222222222219, 122222222222222222220, 122222222222222222221, 122222222222222222222, 122222222222222222223, 122222222222222222224, 122222222222222222225, 122222222222222222226, 122222222222222222227, 122222222222222222228, 122222222222222222229, 1222222222222222222210, 1222222222222222222211, 1222222222222222222212, 1222222222222222222213, 1222222222222222222214, 1222222222222222222215, 1222222222222222222216, 1222222222222222222217, 1222222222222222222218, 1222222222222222222219, 1222222222222222222220, 1222222222222222222221, 1222222222222222222222, 1222222222222222222223, 1222222222222222222224, 1222222222222222222225, 1222222222222222222226, 1222222222222222222227, 1222222222222222222228, 1222222222222222222229, 12222222222222222222210, 12222222222222222222211, 12222222222222222222212, 12222222222222222222213, 12222222222222222222214, 12222222222222222222215, 12222222222222222222216, 12222222222222222222217, 12222222222222222222218, 12222222222222222222219, 12222222222222222222220, 12222222222222222222221, 12222222222222222222222, 12222222222222222222223, 12222222222222222222224, 12222222222222222222225, 12222222222222222222226, 12222222222222222222227, 12222222222222222222228, 12222222222222222222229, 122222222222222222222210, 122222222222222222222211, 122222222222222222222212, 122222222222222222222213, 122222222222222222222214, 122222222222222222222215, 122222222222222222222216, 122222222222222222222217, 122222222222222222222218, 122222222222222222222219, 122222222222222222222220, 122222222222222222222221, 122222222222222222222222, 122222222222222222222223, 122222222222222222222224, 122222222222222			